Studies on Palladium-Catalysed Organic Transformations

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For Melissa

Declaration

I, Mark James Cawley, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Mark Cawley

March 2008

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Abstract

Studies were undertaken to develop a general and practical room temperature protocol for the Buchwald-Hartwig reaction, whereby any aryl halide might be coupled with any N-H moiety using Pd-NHC (*N*-Heterocyclic Carbene) catalysis. Efforts using imidazolium salts, where the Pd-NHC complex is formed *in situ*, resulted in high-yielding reactions of aryl bromides and secondary cyclic amines within 7 h at room temperature, with yields typically in the range of 78-89%. However, only modest yields were obtained with primary amines, secondary acyclic amines and aryl chlorides.

Subsequent research with an isolated (NHC)Pd(R-allyl)Cl complex enabled the efficient high-yielding coupling of a wider range of substrates (including aryl chlorides) in as little as 1 min. The commercially-available base lithium hexamethyldisilazide (LHMDS) was found to be key to the success of both protocols.

Additionally, intramolecular Heck reactions of benzyl halides with pendant olefin chains have also been performed to afford several seven-membered rings with the use of a commercial laboratory microwave reactor. It was possible to effect the cyclisation of 2-(*N*,*N*-homoallyltosylamino)benzyl chloride and (2-chloromethylbenzyl)malonic acid diethyl ester in yields of 98% and 95% respectively yield within 20 min at 90 °C. 2-Homoallyloxybenzyl chloride also underwent reaction in 33% yield at 140 °C.

Acknowledgements

I wish to thank my PhD supervisor, Professor Stephen Caddick, and my industrial CASE supervisors Stuart Pearson and Dr James Scott. I also wish to thank EPSRC and AstraZeneca for the funding of my degree and the technical support staff at University College London for their assistance in the analysis of my samples. I would also like to extend sincere gratitude to all members of the Caddick research group for their invaluable help and support throughout my studies.

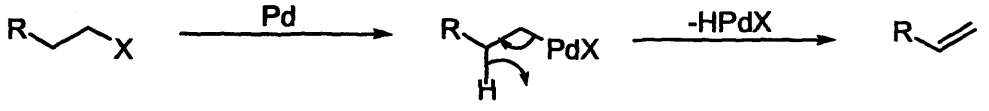
Non-Standard Abbreviations

acac	Acetyl acetone
AIBN	Azobisisobutyronitrile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
dba	Dibenzylideneacetone
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dpph	1,6-Bis(diphenylphosphino)hexane
DMA	*N,N*-Dimethylacetamide
DME	Ethylene glycol dimethyl ether
DMF	*N,N*-Dimethylformamide
EPHP	Ethyl piperidine hypophosphate
HMPA	Hexamethylphosphoramide
IAd.HCl	1,3-Bis(1-adamantyl)imidazolium chloride
It-Bu	1,3-Bis-*tert*-butylimidazol-2-ylidene
It-Bu.HCl	1,3-Bis-*tert*-butylimidazolium chloride
IMes.HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPr	1,3-Bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
IPr.HCl	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolium chloride
LHMDS	Lithium hexamethyldisilazide
MeO-dba	Di-paramethoxybenzylideneacetone
Ms	Mesylate
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NaHMDS	Sodium hexamethyldisilazide
NMP	*N*-Methylpyrrolidone
SIAd.HCl	1,3-Bis-(1-adamantyl)-4,5-dihydroimidazolium chloride
SIMes.HCl	1,3-Bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride
SIPr	1,3-Bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
SIPr.HBF_4	1,3-Bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate
SIPr.HCl	1,3-Bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride
TBAB	Tetra-*n*-butylammonium bromide
TBAC	Tetra-*n*-butylammonium chloride
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBS	*Tert*-butyldimethylsilyl
TBTH	Tributyltin hydride
TTMSS	Tris-trimethylsilylsilane

1.1 Introduction: Palladium-Catalysed Reactions of Saturated Halides

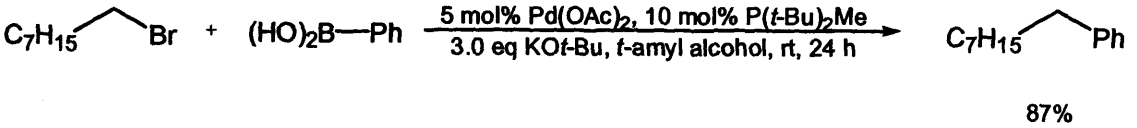
1.1.1. Recent Examples of Palladium-Catalysed Reactions of Saturated Halides

Palladium-mediated coupling reactions have traditionally been limited to the use of aryl or vinyl halides rather than molecules with saturated halides.[1] Not only are saturated halides reluctant to undergo oxidative addition, but if they do, they may then be susceptible to the unwanted competing reaction of β-hydride elimination (Scheme 1).[1,2]



Scheme 1

However, a range of protocols for the palladium-catalysed coupling of alkyl halides in the formation of C-C bonds have been developed over the past ten years. For example, Fu has reported several examples of alkyl halide Suzuki-Miyaura reactions. These reactions use an alkyl phosphine ligand in conjunction with a palladium(II) or palladium(0) source to enable the reactions of alkyl bromides with boronic acids at room temperature (Scheme 2).[3]



Scheme 2

The choice of phosphine was determined to be crucial in this reaction, as early reactions with PCy_3 were moderately successful (Table 1, Entry 1), but the less sterically demanding PCy_2Et saw a significant drop in yield. Interestingly, the highly

bulky P(*t*-Bu)$_3$ was essentially ineffective. Whilst the use of P(*t*-Bu)$_2$Et gave a slight improvement, the steric environment of P(*t*-Bu)$_2$Me was found to afford the highest activity (Table 1, Entry 5).[3]

Table 1: Room temperature Suzuki Couplings of 1-Bromooctane and Phenylboronic acid.[a,3]

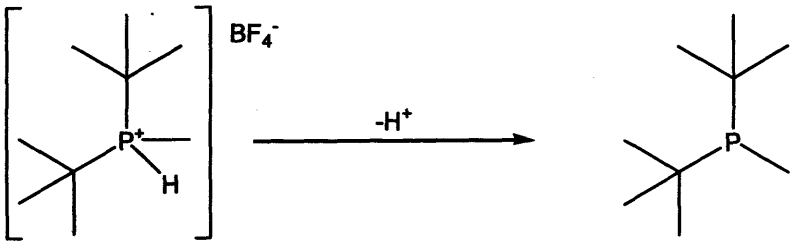
Entry	Ligand	GC yield (%)
1	PCy_3	63
2	PCy_2Et	39
3	P(*t*-Bu)$_3$	<2
4	P(*t*-Bu)$_2$Et	4
5	P(*t*-Bu)$_2$Me	85

[a]Conditions: 1-bromooctane with phenylboronic acid (5 mol% $Pd(OAc)_2$, 10 mol% ligand, 3.0 eq KO*t*-Bu, *t*-amyl alcohol solvent).

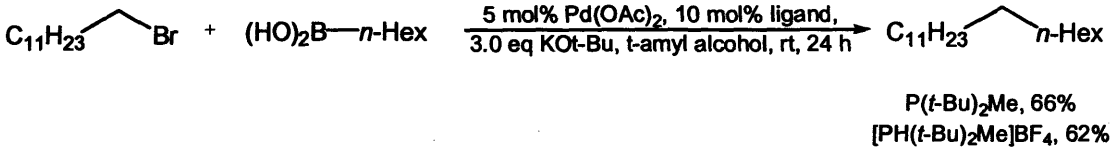
Highly bulky ligands are desirable in palladium-catalysed reactions, as they are reported to promote β–hydride elimination and stabilise the other intermediates in the catalytic cycle.[2] However, too much steric bulk may prevent oxidative addition from occurring, as the palladium centre may be too sterically encumbered to allow further coordination.[2] Such considerations would explain why PCy_3 was more effective than PCy_2Et (preferential reductive elimination) and suggests that P(*t*-Bu)$_2$Et and P(*t*-Bu)$_3$ may have been too bulky to allow facile oxidative addition. The increase in activity from P(*t*-Bu)$_2$Et to P(*t*-Bu)$_2$Me is particularly interesting, as it highlights how apparently slight alterations in substitution (ethyl to methyl) may have a significant bearing on the effectiveness of a ligand in a particular reaction.

Di-*tert*-butylmethylphosphine is somewhat impractical as it is neither air nor moisture stable. However, it was shown that the commercially available salt di-*tert*-butylmethylphosphonium tetrafluoroborate could be used as a shelf-stable alternative,

where deprotonation of the phosphonium cation was believed to generate the phosphine *in situ* (Scheme 3).[3,4] The use of this salt generally afforded similar results to the free ligand, although this was found to vary from one reaction to another (Scheme 4).[3,4]

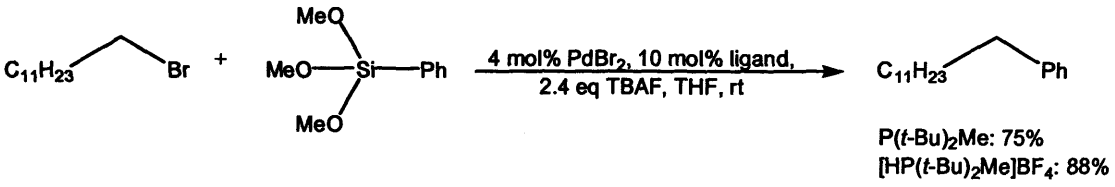


Scheme 3



Scheme 4

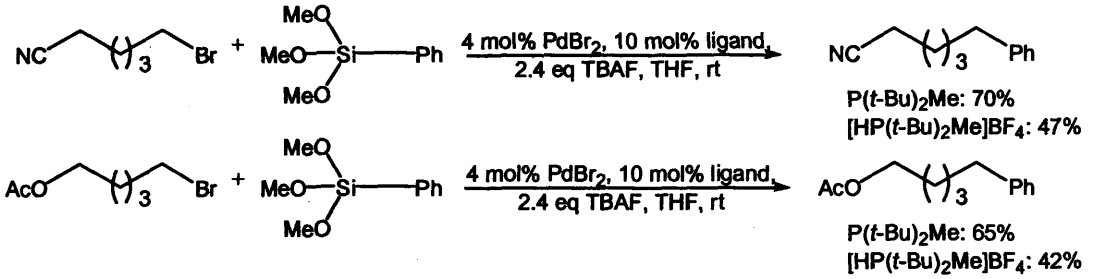
Fu also used P(*t*-Bu)$_2$Me in the room temperature Hiyama coupling of arylsilanes with alkyl bromides and iodides (Scheme 5).[5] In the reaction of 1-bromododecane, the use of [PH(*t*-Bu)$_2$Me]BF$_4$ was actually found to afford a higher yield than P(*t*-Bu)$_2$Me.[5]



Scheme 5

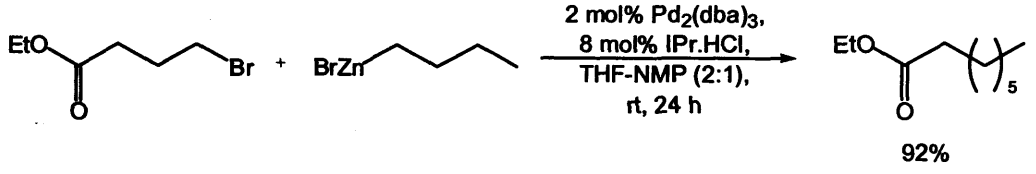
Extensive screening of a number of conditions showed that a system of $PdBr_2$, P(*t*-Bu)$_2$Me and. TBAF was preferred for this reaction. The examination of a wider range of substrates showed that the air-stable phosphonium analogue led to more modest yields for functionalised alkyl bromides (Scheme 6).[5] It appears in these

reactions that there is a trade-off between practicality of the protocol and the isolated yield.



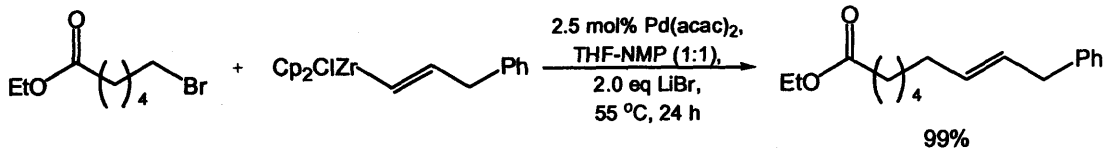
Scheme 6

Not all palladium-catalysed reactions of alkyl halides utilise alkyl phoshine ligands. For example, a Pd-NHC protocol was developed by Organ for the Negishi reaction. Room temperature couplings of unactivated primary alkyl bromides and alkyl organozinc reagents with a wide range of functionality were demonstrated in moderate to high yields (Scheme 7).[6]



Scheme 7

In another interesting example, Fu reported Negishi couplings of alkyl bromides with organozirconium reagents using the simple palladium complex $Pd(acac)_2$, with no need for an additional bulky electron rich ligand, such as an *N*-heterocyclic carbene (NHC) or alkyl phosphine (Scheme 8).[7] These examples illustrate the advances that have been made in this area of chemistry.

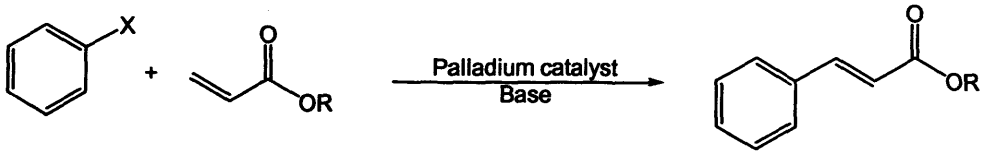


Scheme 8

Despite the many advances in palladium chemistry using alkyl halides, there are few such reported instances of the Heck reaction. However, as this study was carried out in order to develop new methods for this reaction with saturated halides, it is important to discuss the Heck reaction and examples of its use in further detail.

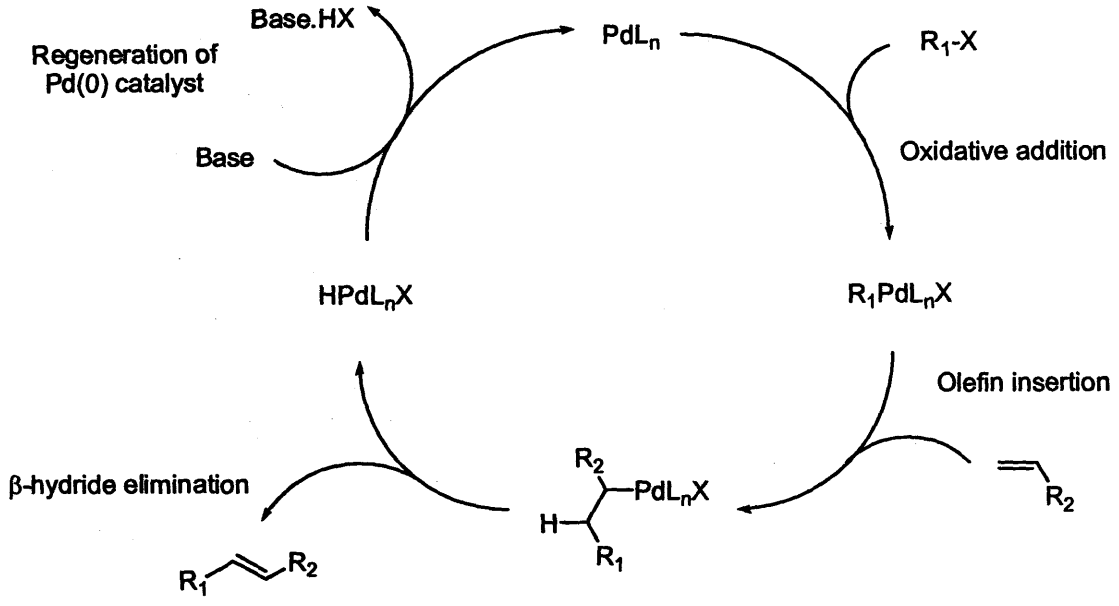
1.1.2. The Heck Reaction

The coupling of an aryl or vinyl halide (or triflate) with an olefin using palladium catalysis in the presence of a base is known as the Heck reaction (Scheme 9).[8] Myriad instances of this reaction have been described in the literature since the 1970s,[1] including intramolecular examples which are used to obtain a variety of different heterocycles.[9]



Scheme 9

The proposed mechanism for the Heck reaction is as follows: following the generation of an active catalytic species, the cycle commences with the rate-determining oxidative addition of the halide to the palladium(0) centre (Scheme 10).[2]



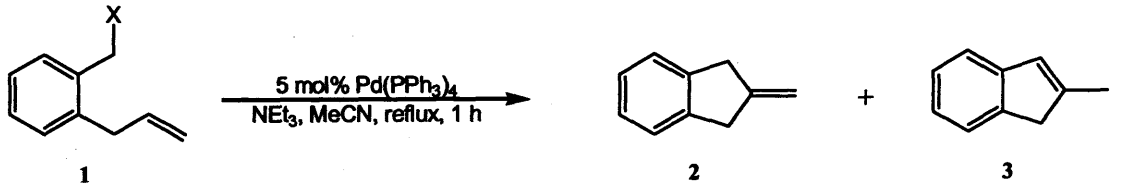
Scheme 10

This is followed by olefin insertion (i.e. carbometallation) to the palladium centre. β-hydride elimination affords the desired coupling product, usually with high *trans* selectivity. Regeneration of the active palladium(0) catalyst species is made possible by deprotonation with the base, which explains the need for stoichiometric or greater amounts of base (Scheme 10).[2,8] A mild base, such as an amine or carbonate salt is usually sufficient to mediate the Heck reaction.

1.1.3. Palladium-Catalysed Intramolecular Heck Reactions of Saturated Halides

A protocol for the intramolecular Heck reaction was described by Negishi regarding the use of benzyl halides (compounds where the halide leaving group is bonded to a saturated sp^3 carbon centre, but *without* β–hydrogens).[10] Negishi showed that, upon treatment with sub-stoichiometric amounts of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, benzyl halides with pendant olefin chains underwent the intramolecular Heck reaction to deliver five-, six- and seven-membered carbocycles (Scheme 11).[10] The retention of the alkene regiochemistry was also noted in most cases.

For example, several variants of **1** were manipulated into mixtures of 2-methyleneindan **2** and of 2-methylindene **3**. The observation was made that the choice of leaving group could affect both the ratio of products formed as well as the reaction time (Table 2).[10]



1 **2** **3**

Scheme 11

An interesting observation is the relative reaction times of the benzyl chloride and bromide (Table 2, Entries 1-2). It appears that the only disadvantage of using the chloride as a precursor is the slightly longer reaction time, although it is notable that the yields are identical. In both cases only negligible levels of the isomeric product **3** were isolated.

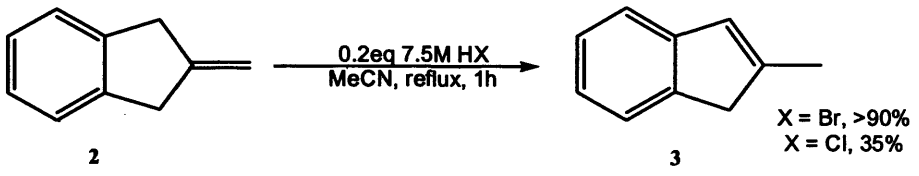
Table 2: Effect of Leaving Group X in the Intramolecular Heck reactions of **1**[a,10]

Entry	X	% Yield **2**	% Yield **3**	Reaction Time
1	Cl	82	<1	1 h
2	Br	82	<1	0.5 h
3	Br	68	17	1 h
4	I	64	18	0.5 h
5	Oms	60	<1	1 h
6	OCO_2Me	26	23	5 days
7	Oac	<1	<1	2 days

[a]Conditions: 5 mol% $Pd(PPh_3)_4$, 2.0 eq NEt_3, MeCN, reflux.

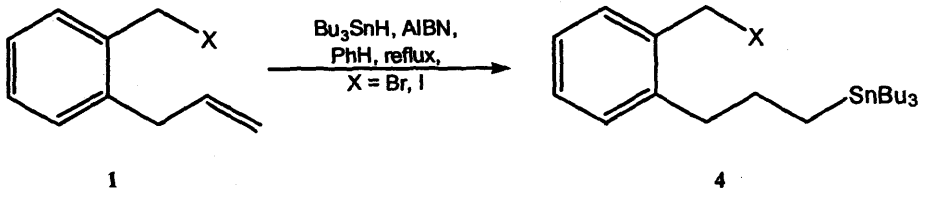
A further difference was noted between the chloride and bromide substrates when the reaction times were prolonged. After 1 h, the bromide gave yields of 68% and 17%

for **2** and **3** respectively (Table 2, Entry 3).[10] On the other hand, little isomerisation was observed for the benzyl chloride even after 3 h under the same conditions.[10] This trend continued with the iodide substrate, affording a mixture after only 0.5 h (Table 2, Entry 4). As treatment of **2** with 0.2 equiv of 7.5 M HBr in refluxing acetonitrile led to complete isomerisation into **3** in over 90% yield within 1 h, Negishi noted that it was a possibility that isomerisation was acid-catalysed rather than Pd-catalysed. The addition of 7.5 M HCl only induced isomerisation of **2** to **3** in a yield of 35% under similar conditions, appearing to show that isomerisation was of more significance in the presence of Br^- (Scheme 12).[10] However, Negishi did not report whether further heating past 1 h in the presence of HCl would lead to a greater conversion of **2** into **3**, which would have shown whether the disparity in yield was due to differences in kinetics or reactivity.



Scheme 12

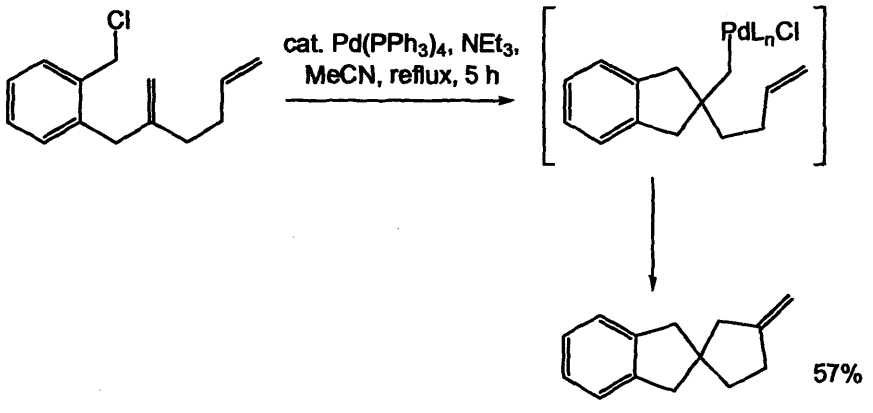
Attempts to perform the cyclisation of the iodide and bromide analogues of **1** under tin-mediated free-radical conditions failed, giving only the corresponding hydrostannylation product **4** (Scheme 13). This showed that palladium chemistry did not merely complement tin chemistry, but that it had the potential even to supersede it altogether.[10]



1 4

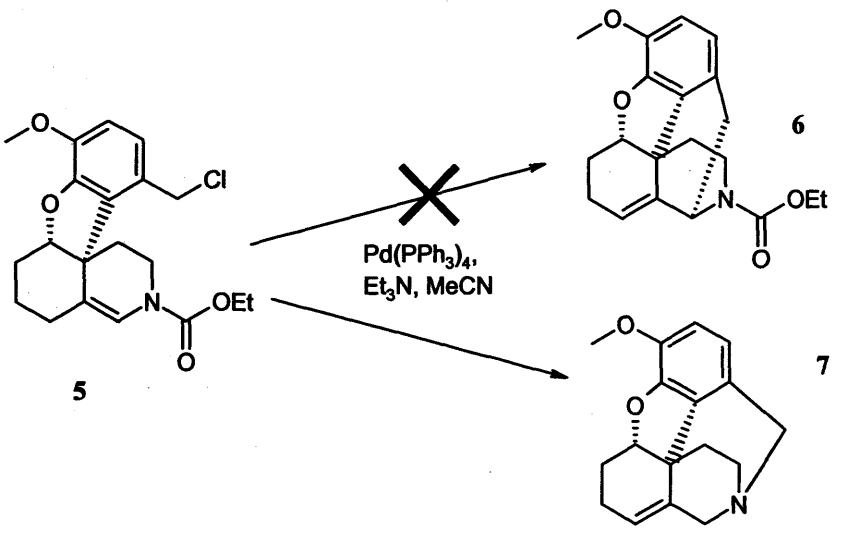
Scheme 13

Negishi also outlined several other examples, including a cascade reaction where the carbometallation intermediate underwent further reaction with a second olefin group rather than undergoing reductive elimination (Scheme 14).[10] However, Negishi did not extend this methodology to include the preparation of heterocycles.



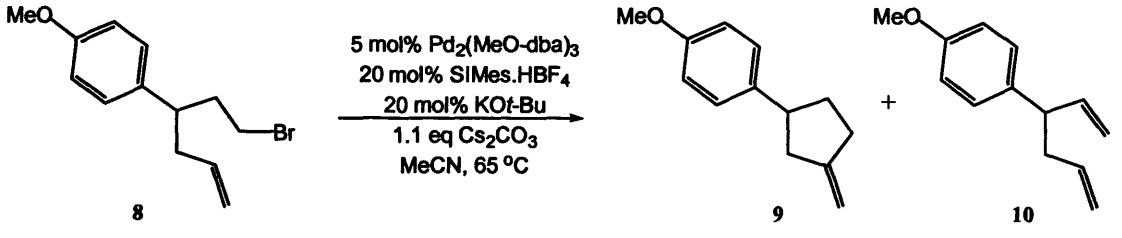
Scheme 14

Curiously, no significant developments for the intramolecular Heck reaction of benzyl halides appeared after 1989. In fact, in a review in 1996, Negishi wrote that: "Although underdeveloped, this reaction appears to hold considerable promise as a synthetic tool."[11] Since then there have been a only few reports of attempts to develop such reactions. One example was reported by Cheng in 2000 whilst working on an approach towards the construction of the morphine skeleton. When the intermediate **5** was subjected to the Heck reaction conditions employed by Negishi, rather than giving the anticipated compound **6**, an intramolecular *N*-benzylation occurred, leading to the tertiary amine **7** (Scheme 15).[12]



Scheme 15

A very important milestone in the Heck reaction was reached in late 2007, when Fu described the intramolecular Heck reaction of unactivated alkyl halides with β–hydrogens.[13] In the reaction of the alkyl halide **8**, it was determined that a Pd-NHC catalyst (where the NHC was formed *in situ* from an imidazolinium salt) possessed the desired reactivity profile to maximise the formation of the ring **9**, whilst suppressing the formation of the elimination product **10** (Scheme 16; Table 3).[13]

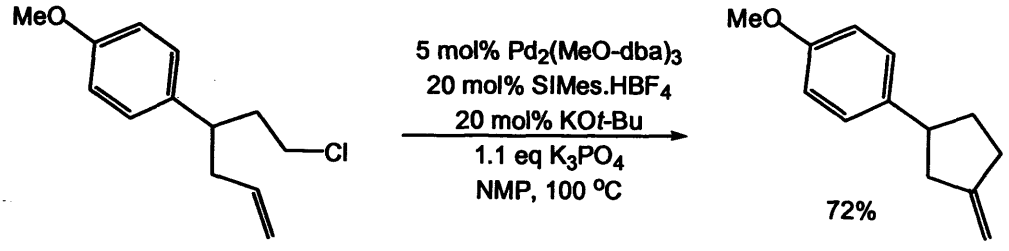


Scheme 16

Fu examined a variety of conditions, with a focus on variation of NHC and trialkylphosphine ligands. (Table 3, Entries 1-5) The imidazolium salt SIMes.HBF_4 was determined to be the optimum ligand for this reaction, in conjunction with an equivalent amount of the strong base KO*t*-Bu. It is believed that the base is necessary to deprotonate the imdazolium salt in order to form the active NHC *in situ* (See

section 1.2 on NHCs). It appeared that the mild base caesium carbonate (Cs_2CO_3), used to regenerate the Pd(0) active species, was insufficiently strong to deprotonate SIMes.HBF_4 at 65 °C.[13] Nonetheless, in the absence of any ligand, low conversion to **9** and **10** was observed (Table 3, Entry 6). Additionally, it was demonstrated that the nature of the palladium source was also of significance: the Pd_2(MeO-dba)$_3$ adduct was found to afford a improved yield in comparison to the unfunctionalised $Pd_2(dba)_3$ (Table 3, Entry 7).[13]

Using this methodology, Fu was able to isolate several five-membered carbocycles, with both aryl and non-aryl substituents in the homoallylic position. It was even possible to catalyse the reactions of unactivated alkyl chlorides with β-hydrogens, although more heating was necessary to enable these examples (Scheme 17).[13]



Scheme 17

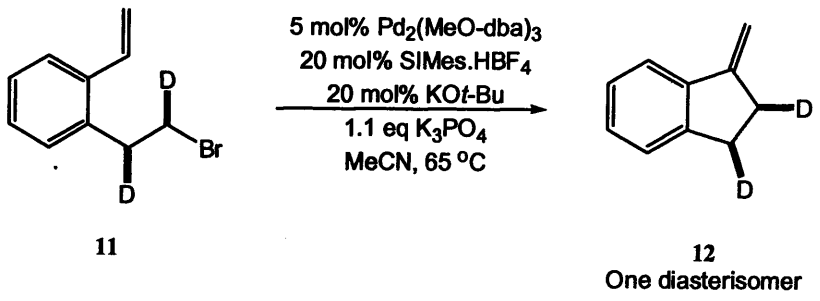
However, one potential drawback of this methodology is its reliance on the relatively strong base KO*t*-Bu in order to deprotonate the imidazolium salt SIMes.HBF_4. This reagent may limit the versatility of the reaction, as it may not be compatible with fragile functional groups that would normally withstand the mildly basic conditions of the Heck reactions. As such, further research may be required to allow more facile access to the active catalytic species.

Table 3: Influence of Reaction Conditions in the Intramolecular Heck Reaction of an unactivated alkyl halide **8**[a]

Entry	Pd	Ligand	Base	Solvent	GC Yield **9**/%	GC Yield **10**/%
1	$Pd_2(MeO\text{-}dba)_3$	SIMes.HBF_4/KO*t*-Bu	Cs_2CO_3	MeCN	80	6
2	$Pd_2(MeO\text{-}dba)_3$	IMes.HBF_4/KO*t*-Bu	Cs_2CO_3	MeCN	13	5
3	$Pd_2(MeO\text{-}dba)_3$	SIPr.HBF_4/KO*t*-Bu	Cs_2CO_3	MeCN	27	20
4	$Pd_2(MeO\text{-}dba)_3$	P(*t*-Bu)$_2$Me	Cs_2CO_3	MeCN	43	52
5	$Pd_2(MeO\text{-}dba)_3$	PCy_3	Cs_2CO_3	MeCN	53	23
6	$Pd_2(MeO\text{-}dba)_3$	-	Cs_2CO_3	MeCN	<2	2
7	$Pd_2(dba)_3$	SIMes.HBF_4/KO*t*-Bu	Cs_2CO_3	MeCN	44	50
8	-	SIMes.HBF_4/KO*t*-Bu	Cs_2CO_3	MeCN	<2	<2
9	$Pd_2(MeO\text{-}dba)_3$	SIMes.HBF_4/KO*t*-Bu	K_3PO_4	MeCN	37	8
10	$Pd_2(MeO\text{-}dba)_3$	SIMes.HBF_4/KO*t*-Bu	Cs_2CO_3	NMP	46	15

[a]Conditions: 5 mol% $Pd_2(MeO\text{-}dba)_3$, 20 mol% ligand, 1.1 eq base, 65 °C

In order to determine whether this protocol utilised a radical or ionic mechanism, the reaction of the deuterium-labelled alkyl halide **11** was investigated. Cyclisation of **11** afforded only one diastereoisomer **12** (Scheme 18), which Fu claimed was consistent with an S_N2 oxidative addition step, arguing that a radical pathway would result in a mixture. However it may also be possible that oxidative addition occurred *via* a concerted process which could also potentially only afford one product.[13] According to Fu, these findings appeared to rule out any free-radical intermediates (as in Heck-type reactions with other metals such as nickel (*vide infra*)) and were instead consistent with other palladium-catalysed reactions.[13]

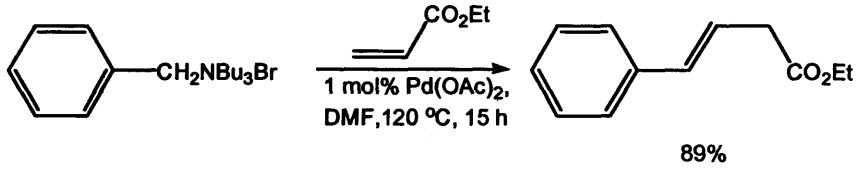


11 **12**
One diasterisomer

Scheme 18

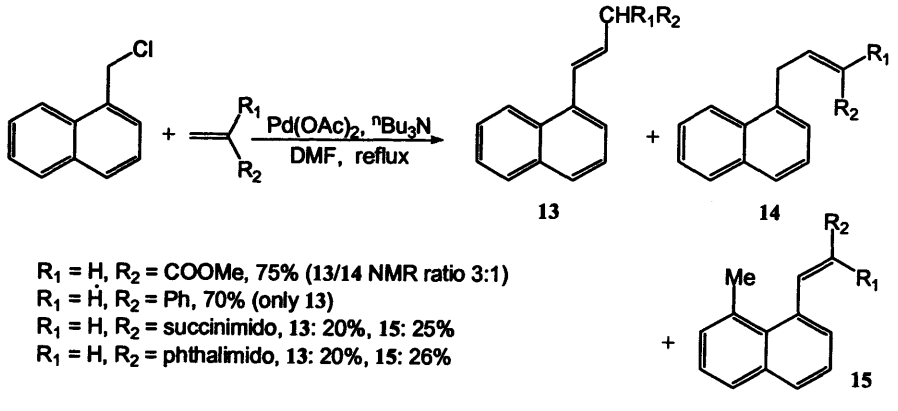
1.1.4. Palladium-Catalysed Intermolecular Heck Reactions of Saturated Halides

Intermolecular Heck reactions of saturated halides have also been described in the literature. Research was conducted in this area by Pan following early success in the Heck-type vinylation of benzylic quaternary ammonium salts with palladium acetate (Scheme 19).[14]



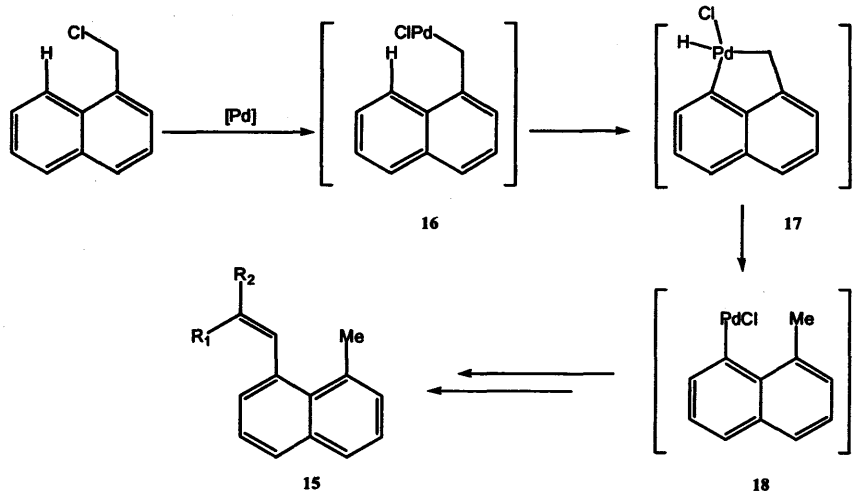
Scheme 19

In subsequent research, the palladium catalysed reaction of α-chloromethylnaphthalene was found to generally afford the coupling products **13** and **14** with several alkenes, showing the reactivity profile that might be expected for benzyl halides.[15] Whilst **14** was the normal coupling product of the Heck reaction, its isomer **13** was usually formed in greater quantities due to the stability of the conjugated system. However, the reactions of *N*-vinylsuccinimide and *N*-vinylphthalimide afforded an additional product **15**, where the olefinic species was attached to the *peri* position of the naphthalene ring (Scheme 20).[15]



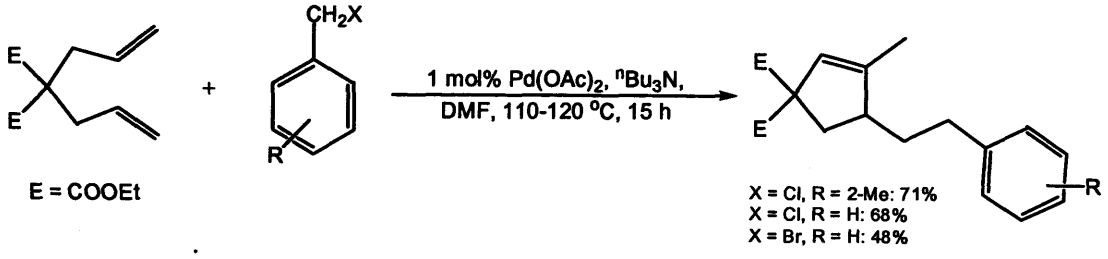
Scheme 20

It was believed that **15** was formed through the cyclopalladation of the oxidative addition intermediate **16** to give **17**. It was assumed that *N*-vinyl olefins were able to stabilise **17** as coordinative ligands, allowing enough time for cyclopalladation to occur, forming **18** and ultimately the final product **15**. (Scheme 21).[15]



Scheme 21

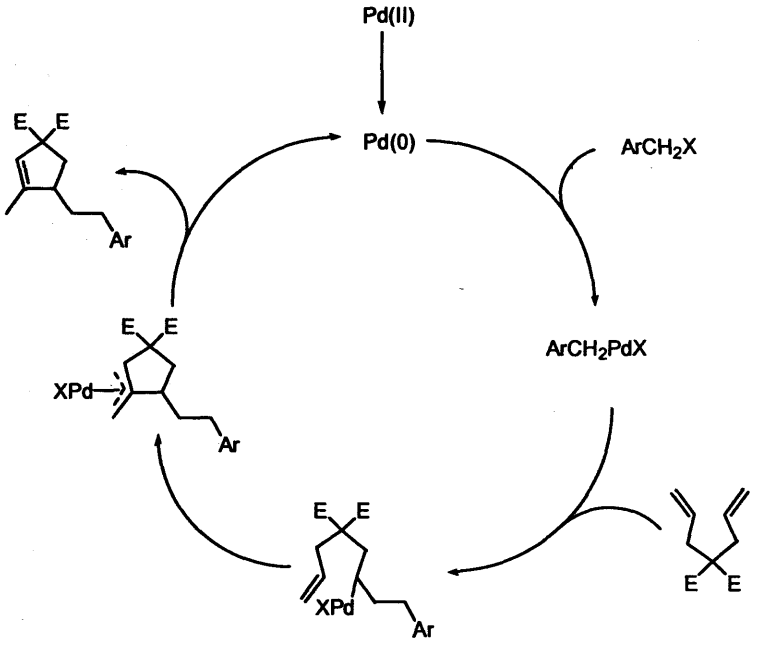
In 2003, Pan outlined how a number of substituted cyclopentene rings could be formed when benzyl halides were treated with diethyl diallylmalonate under palladium catalysis. Generally, a mixture of the malonate was found to react with a benzyl bromide or chloride with tributylamine as base and palladium(II) acetate as catalyst, affording cyclopentene derivates in moderate yields (Scheme 22).[16]



Scheme 22

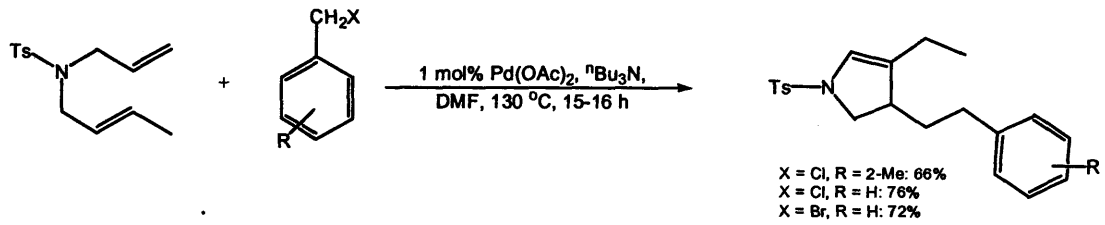
Electron-donating phenyl substituents were found to promote the reaction, resulting in higher yields. Electron-withdrawing groups hindered the reaction, with *p*-nitrobenzyl chloride failing to react. Efforts were concentrated on benzyl chlorides, as they were determined to be the most reactive under these conditions, with benzyl bromide giving a lower yield of the Heck product than benzyl chloride (Scheme 22). These trends are the opposite of what might be expected in the palladium-catalysed reactions of aryl halides (where oxidative addition is believed to be concerted),[16] possibly indicating a different mechanism of oxidative addition for saturated halides (most likely S_N2).[13] However, more facile oxidative addition to benzyl chlorides is also at odds with Negishi's findings for his intramolecular reactions (Table 2) and with the findings from Fu's work on alkyl halides (*vide supra*), particular as Br^- is a better leaving group than Cl^- in an S_N2 reaction. As Pan reported equivalent reaction times for all substrates, it is worth considering the possibility that in the reaction of benzyl bromide, the cyclopentene might be fully prepared in less than 15 h, but that decomposition of the product could occur during excess heating above 100 °C, possibly explaining the lower isolated yield.

Pan hypothesised that the reaction consisted of the palladium-catalysed reaction between the benzyl halide with the olefinic moiety, followed by an intramolecular cascade coupling. Oxidative addition to palladium(0) was believed to be followed by addition to one of the double bonds, generating an organopalladium intermediate, which then added to the other double bond, forming the cyclic structure. Whilst such an organopalladium intermediate would possess β-hydrogens, addition to the second bond was deemed preferable over elimination (Scheme 23).[16]



Scheme 23

More recently, Pan also reported the coupling of benzyl halides with *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide under similar conditions to those used with diethyl diallylmalonate (Scheme 24).[17] Again, benzyl chlorides with electron-donating groups on the phenyl ring afforded the highest yields. Electron-withdrawing groups (e.g. CO_2Me and Br) hindered the reaction, affording the lowest yields. Pan suggested that the reaction progressed *via* a similar sequence of coupling followed by cyclisation.[17] Pan noted that these cascades were the first Heck reactions of benzyl halides with β-hydrogens where β-hydride elimination did not occur at the earliest opportunity.[16,17]

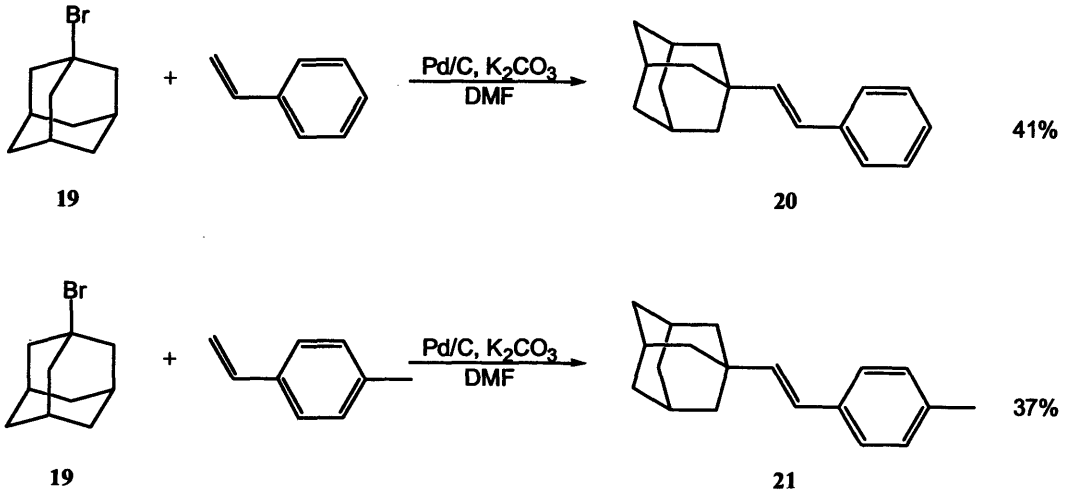


Scheme 24

In addition to Pan's endeavours with benzyl chlorides, Waegell and de Meijere reported the intermolecular Heck reaction of an alkyl halide with selected olefins.[18]

Having realised the potential difficulty of β-hydride elimination on the bridgehead of an oligocyclic hydrocarbon such as adamantane, Waegell and de Meijere postulated that it should be possible to observe Heck reactions of bridgehead halides.[18] As a related Sonogashira reaction protocol was not successful using iodocubane,[19] 1-bromoadamantane **19** was examined as a potential coupling partner.

It was found that **19** would undergo the Heck reaction with selected olefins in low to moderate yields using a catalyst of palladium on charcoal, with the reactions of styrene and *para*-methylstyrene solely affording the *trans*-olefin products **20** and **21** in yields of 41% and 37% respectively (Scheme 25).[18]



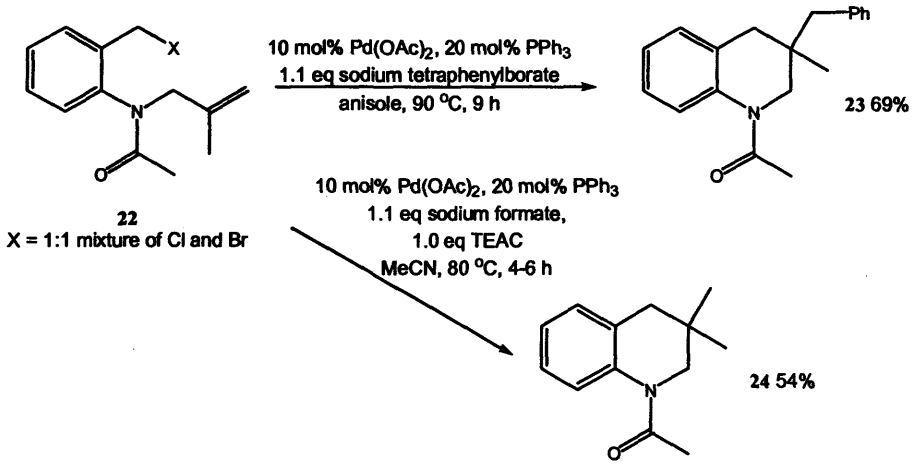
Scheme 25

1.1.5. Heck-Type Tandem Cyclisation-Anion Capture with Saturated Halides

In 1989, Grigg developed a protocol related to the Heck reaction for selected vinyl or aryl halides with pendant alkene, alkyne or diene chains. This was a tandem cyclisation-anion capture process that did not involve the β–hydride elimination step of the standard Heck reaction.[20]

Under this protocol, the halide substrates would undergo oxidative addition to palladium, followed by regio- and stereospecific cyclisation. Due to the resulting alkyl-, vinyl-, or π–allyl-palladium species not having any available *syn*-β–hydrogens to allow elimination, they would then be intercepted by an "anion" transfer agent.[20]

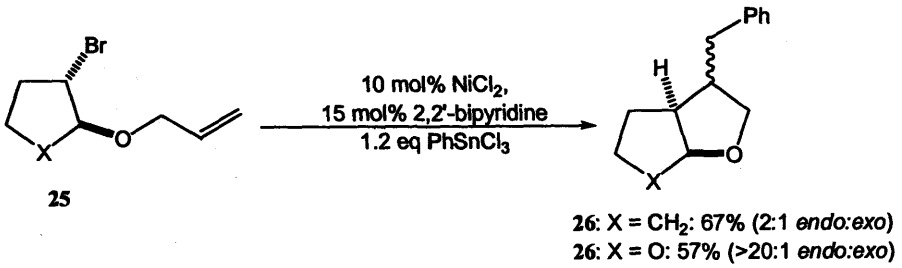
For example, it was demonstrated that the benzyl halide **22** reacted with sodium tetraphenylborate (Ph^- source) in the presence of Pd(0) to afford **23**. A similar reaction with sodium formate (hydride source) afforded **24** (Scheme 26).[20,21]



Scheme 26

1.1.6. Heck-Type Reactions of Saturated Halides *via* Radical Intermediates

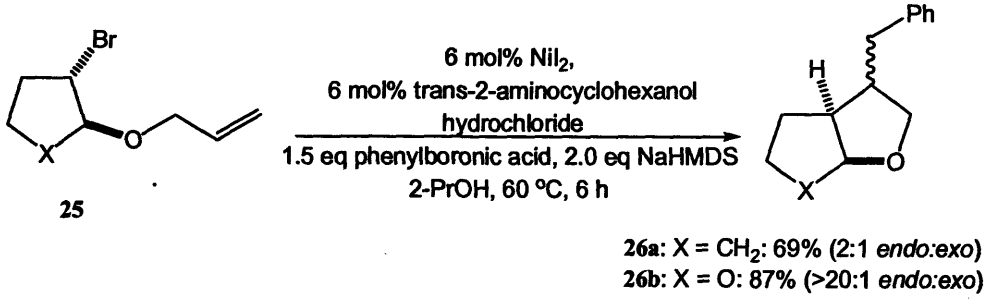
Heck-type reactions have also been reported using other transition metals. For example, reactions of unactivated secondary alkyl halides with pendant olefin chains using nickel catalysis were described by Fu in 2004.[22] In this study, alkyl bromides of the type **25** first underwent intramolecular Heck-type cyclisations, which were followed by intermolecular cross-coupling with an organotin compound to afford *cis*-fused 5,5 ring systems **26** (Scheme 27).[22]



Scheme 27

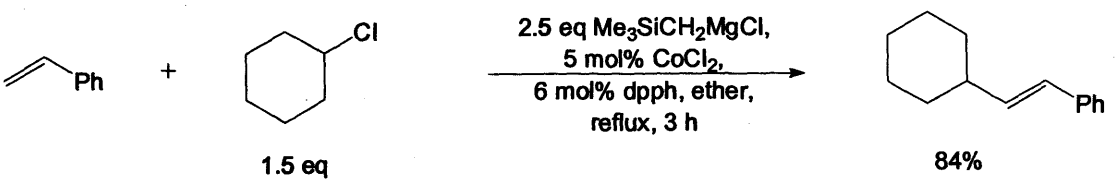
It was observed that when **26** had a cyclopentane core that it was obtained with a much lower *endo/exo* ratio than with the corresponding tetrahydrofuran (*endo/exo* ratio of >20:1). Fu hypothesised that these reactions were possibly a result of an initially formed secondary alkyl radical species that would cyclise prior to its reaction with nickel. Fu claimed that this was supported by the diastereoselectivities observed for these substrates being independent of ligand structure, as several ligands were screened in addition to 2,2'-bipyridine.[22] However, further investigation of the mechanism was not reported.

Similar reactivity was found in the nickel-catalysed Heck-Suzuki reactions of **25**, where the coupling was performed instead with a boronic acid. The diastereoselectivities were essentially equivalent to those observed in the Stille reactions, leading Fu to reassert the hypothesis of a radical species being involved in the oxidative addition step (Scheme 28).[23]



Scheme 28

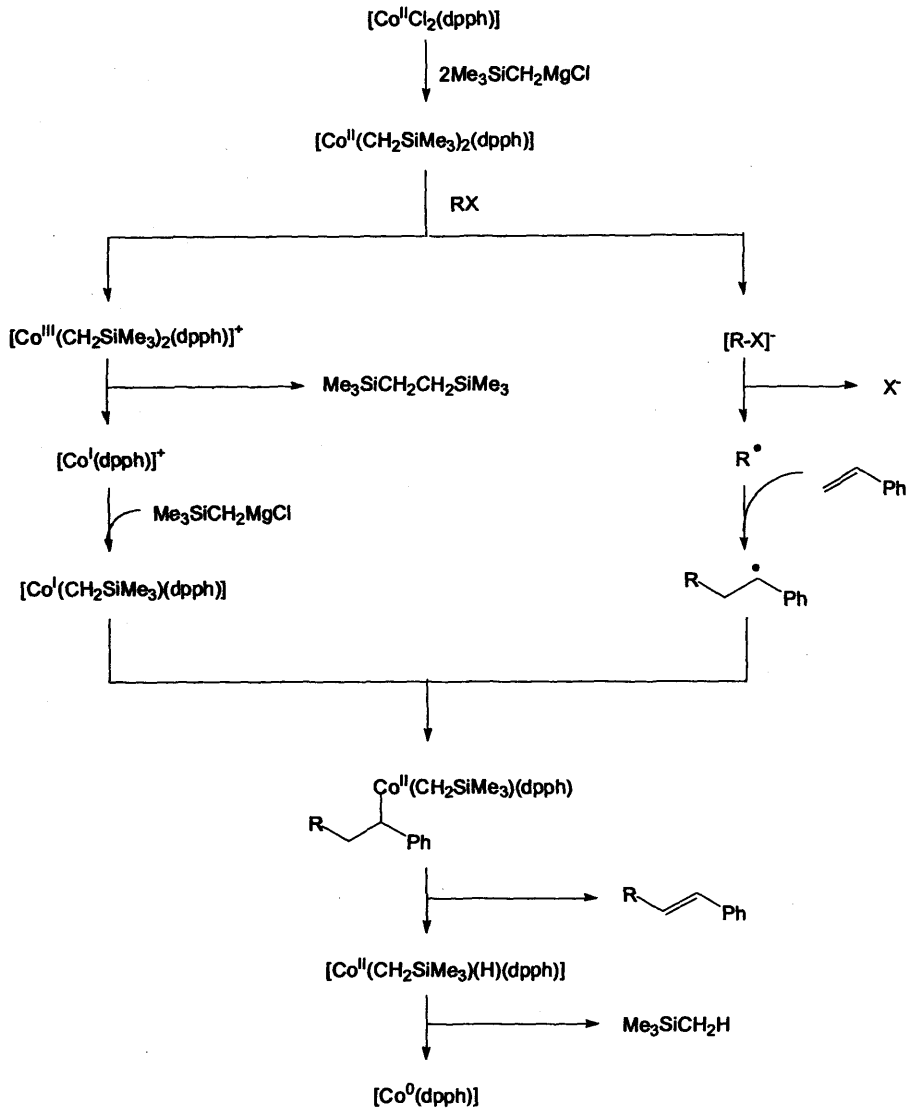
In 2002 Oshima reported the cobalt-catalysed styrylation of a range of alkyl halides in the presence of the trimethylsilylmethylmagnesium chloride Grignard reagent, Me_3SiCH_2MgCl (Scheme 29).[24,25]



Scheme 29

As well as a suitable phosphine ligand for the cobalt metal centre, it was determined that the Grignard reagent was necessary for the reaction to take place. A mechanistic study suggested that the cobalt-catalysed reaction consisted of both an initiation step to furnish the active catalyst [Co^0(dpph)] (which also formed some of the coupling product) and then a catalytic cycle where the bulk of the styrylation occurred.[24,25]

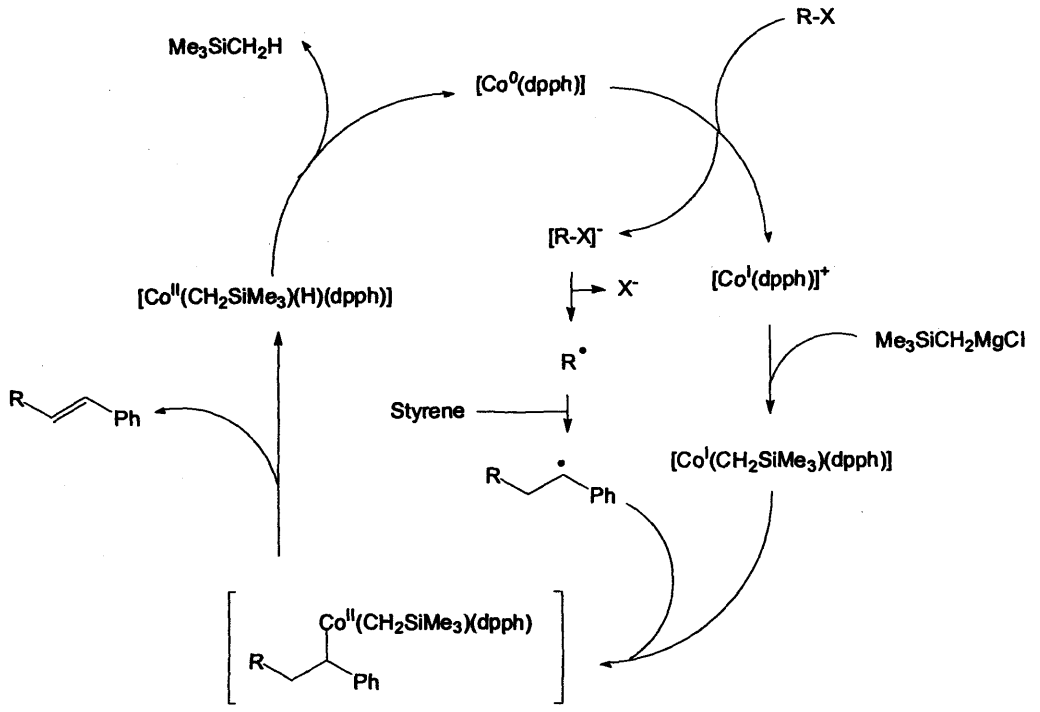
The initiation step begins with the reaction of [$Co^{II}Cl_2$(dpph)] and Me_3SiCH_2MgCl affording [$Co^{II}(CH_2SiMe_3)_2$(dpph)]. This then undergoes single electron-transfer to give [Co^{I}(dpph)]$^+$ and the alkyl radical. The 12-electron cationic [Co^{I}(dpph)]$^+$ is highly electron deficient, meaning that it immediately reacts with the Grignard reagent Me_3SiCH_2MgCl to give [$Co^{I}(CH_2SiMe_3)$(dpph)] (Scheme 31).[24,25] This complex captures the benzyl radical formed through the addition of the alkyl radical to styrene. β-Elimination giving the Heck-type product is followed by rapid reductive elimination of $SiMe_4$ leaving [Co^0(dpph)], which is the active species for the catalytic cycle (Scheme 30).[24,25]



Scheme 30

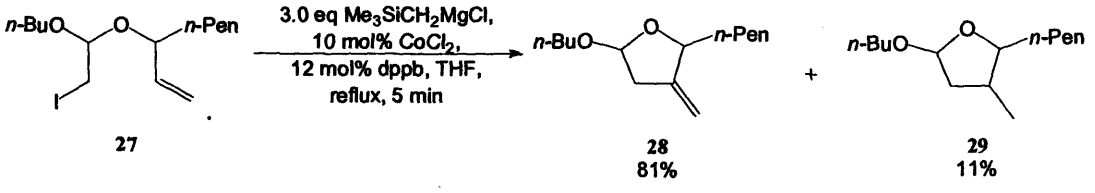
Oshima hypothesised that the catalytic cycle consists of steps similar to those found in the initiation step (Scheme 31). However, the only difference in the catalytic cycle is that reductive elimination does not occur after single electron transfer. This is because the electron donor, $[Co^0(dpph)]$, possesses no Me_3SiCH_2 groups. Instead an ate complex, $[Co^0(CH_2SiMe_3)(dpph)]MgCl$ effects single electron transfer (this is formed from $[Co^0(dpph)]$ and one equivalent of the Grignard reagent – not shown in Scheme 31). Alternatively, neutral $[Co^I(CH_2SiMe_3)(dpph)]$ would be directly produced after the single electron transfer, capturing the benzylic radical (Scheme 31). However,

Oshima still noted the possibility that the reaction might proceed *via* Co^{I} or Co^{III} species instead.[24,25]



Scheme 31

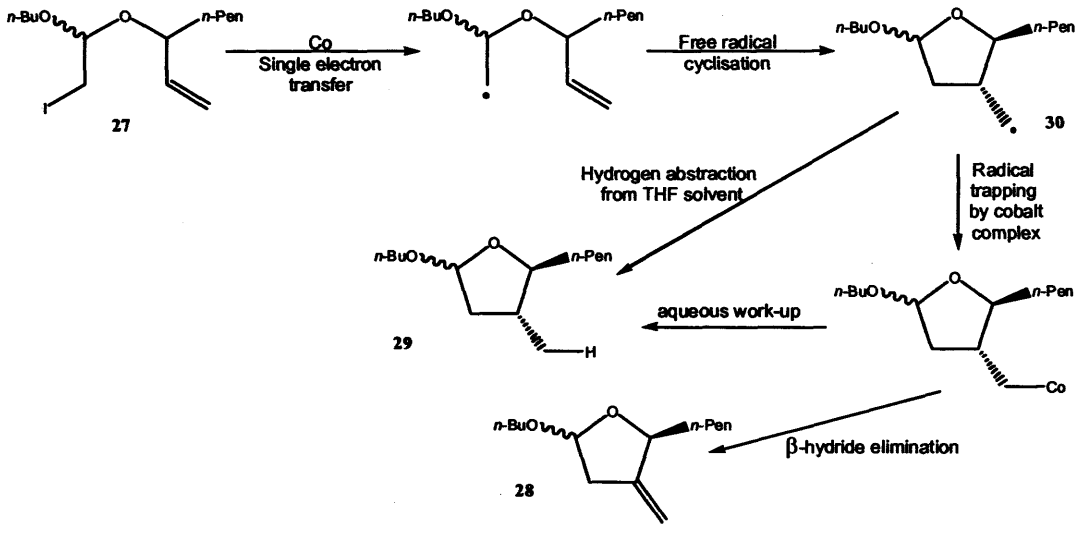
Shortly after, Oshima also reported the intramolecular Heck-type reaction of 6-iodo-1-hexene derivatives and the trimethylsilylmethylmagnesium chloride Grignard reagent with $CoCl_2$(dppb) catalysis in refluxing THF to afford a range of methylenecyclopentanes.[24,25] For example, the reaction of **27** afforded **28** in 81% yield (Scheme 32). However, 11% of the saturated product **29** was obtained. Oshima claimed that the formation of **29** again suggested a radical cyclisation pathway and that **28** was also obtained *via* a radical intermediate.[24,25]



27 **28** 81% **29** 11%

Scheme 32

Oshima hypothesised that the reaction began with the formation of the radical intermediate through cobalt-mediated single electron transfer. Free radical cyclisation to give **30** was followed by trapping with a cobalt complex and β–hydride elimination to afford the Heck-type product **28** (Scheme 33).[25]

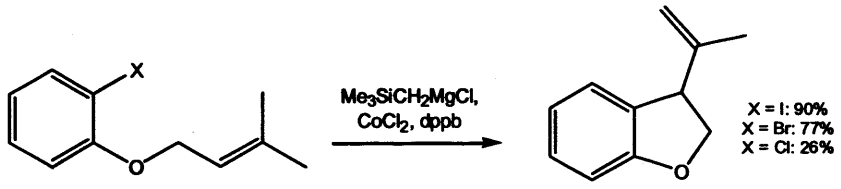


Scheme 33

The saturated product **29** was formed through H-abstraction by **30** from the THF solvent and from the aqueous work up of the cobalt complex formed through radical trapping.[25] Oshima did not report the intramolecular reactions of alkyl bromides or chlorides, which was an interesting omission considering that intermolecular reactions were possible with alkyl bromides and chlorides.[24,25] This appeared to suggest that facile intramolecular reactions for a range of substrates might only be possible with alkyl iodides.

However, the same protocol has also been used with success in the intramolecular Heck-type reaction of aryl halides (Scheme 34). It was explained by Oshima that aryl halides are likely to undergo oxidative addition to form aryl-cobalt bonds in an analogous fashion to oxidative addition of palladium to aryl halides, rather than *via*

the generation of an aryl radical *via* a single electron-transfer process which would not generate the isopropenyl-substituted heterocycle.[24,25,26]



Scheme 34

1.1.7. Summary

It is clear that many major advances have been made in recent years in palladium-catalysed cross coupling reactions, particularly with alkyl halide substrates. Considering the promise of reported methods, such as the intramolecular protocol for carbocycle synthesis reported by Negishi,[10] a study has been undertaken to develop new routes to other important compounds. Fu's protocol for the formation of carbocycles (published in 2007 after this study was completed)[13] has been further indication of the potential of alkyl halides in the Heck reaction.

Notwithstanding the achievements reported in the literature, there is still a significant lack of development in the Heck reaction, particularly in its application to heterocycle synthesis. However, due to the regular occurrence of heterocyclic moieties in biologically active molecules, new protocols for their preparation would be highly valued indeed. Therefore, the study has focused on the preparation of heterocycles *via* the Heck reaction of saturated halides. This research has been carried out despite the relatively non-trivial preparation of certain heterocycles in comparison to their carbocyclic analogues (*vide infra*).

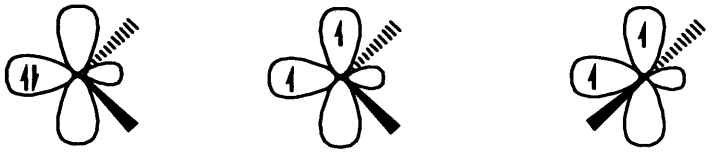
1.2. *N*-Heterocyclic Carbenes (NHCs) as Ancillary Ligands in Palladium Catalysis

1.2.1 Carbenes

A *carbene* is a compound possessing a carbon centre with two substituents and a pair of non-bonding electrons (Scheme 35).[27] Carbenes have no formal charge but are often drawn as zwitterions with both a positive and negative charge on the carbon centre to represent how they are susceptibile to electrophilic and nucleophilic attack.[28]

Scheme 35

Carbenes exist in two different energy states. In the *singlet* state, the carbon centre is sp^2 hybridised. The two substituents and the electron pair exist in the same plane, above and below which is an empty *p*-orbital (Scheme 36).[27] In the *triplet* state, the carbon centre is commonly sp^2 hybridised, but in some cases may be sp hybridised (Scheme 36). In either form of the triplet state, the two electrons are unpaired, existing in two different *p*-orbitals.

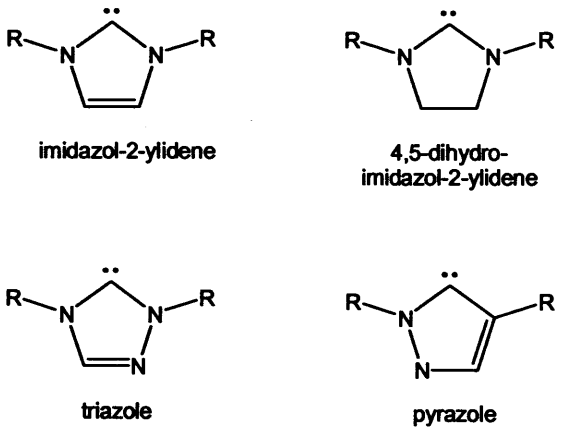


Scheme 36

Normally, carbenes are quite unstable, and often only exist very briefly as intermediates or as reagents generated *in situ*. As such, they have traditionally only been observed as a result of their reactivity.[29]

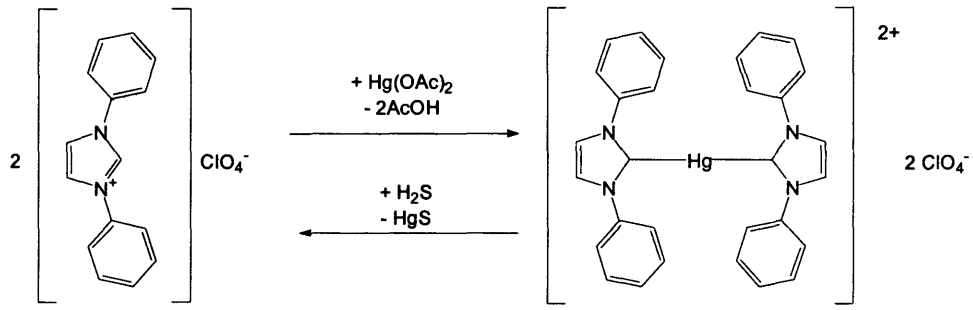
1.2.2 Development of *N*-Heterocyclic Carbenes (NHCs).

Some carbenes may be stable under certain conditions, existing either as free carbenes or in complexes with transition metals.[27] An important class of stable carbene is the N-*heterocyclic carbene* (NHC).[30] Common examples of NHC include imidazol-2-ylidenes, 4,5-dihydroimidazol-2-ylidenes, triazoles and pyrazoles (Scheme 37).[30]



Scheme 37

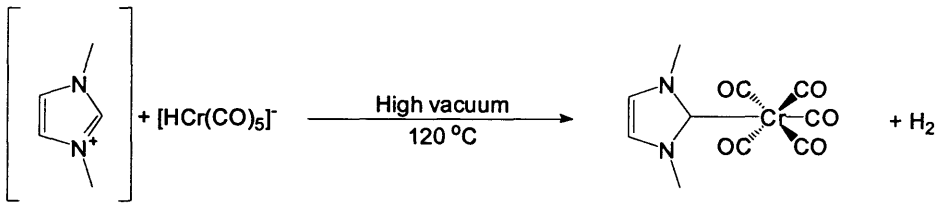
The first transition metal-NHC complexes were prepared independently by Wanzlick[31] and Öfele[32] in 1968. Wanzlick added mercury(II) acetate to 1,3-diphenylimidazolium perchlorate **31** in the polar solvent DMSO to afford the carbene, bis(1,3-diphenylimidazolio)mercury diperchlorate **32**, liberating near quantitative amounts of acetic acid.[31] The mercury-NHC complex **32** was found to be inert under acidic conditions, but would revert to the imidazolium salt **31** when treated with hydrogen sulfide (Scheme 38).[31]



31 **32**

Scheme 38

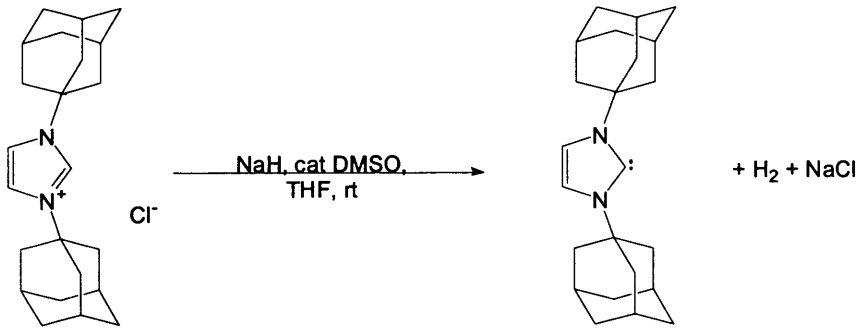
By sublimation of the imidazolium salt **33** in a high vacuum at 120 °C, Ofele managed to prepare and characterise the chromium-NHC complex **34** (Scheme 39).[32]



33 **34**

Scheme 39

Despite these endeavours, a free persistent carbene was not isolated as a crystalline solid until the pioneering work of Arduengo in 1991.[33] Arduengo showed how deprotonation of the imidazolium salt **35** was possible with one equivalent of sodium hydride and catalytic amounts of the dimsyl anion ($^{-}CH_2S(O)Me$) at room temperature, to give the free NHC 1,3-(di-1-adamantyl)imidazol-2-ylidene **36** (Scheme 40).[33]



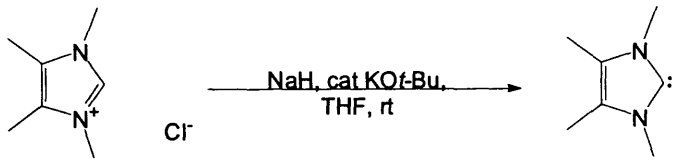
35 **36**

Scheme 40

36 was stabilised by favourable electronic factors which consisted of π-donation into the out-of-plane *p* orbital of the carbene by the electron-rich π–system (N-C=C-N).[33] These π–interactions resulted in several resonance forms where the positive charge was delocalised across the imidazole ring, with the C_2 carbon centre (i.e. that between the nitrogen atoms) effectively a carbanion centre. Arduengo hypothesised that further electronic stability arose as a result of the carbene being between the two electronegative nitrogen centres. As such favourable electronics had not previously been sufficient to afford a stable crystalline carbene, Arduengo also asserted that the high steric bulk afforded by the adamantyl groups was key to the kinetic stability of the carbene, but that sufficient room remained for chemical reactions to occur at the carbene centre.[33]

Further studies caused Arduengo to re-evaluate his hypotheses.[34] Although the high stability of **36** *was* partially as a result of the steric protection of the adamantyl groups, electronic stabilisation of the carbene centre from the imidazol-2-ylidene ring was found to be sufficient to afford a stable and isolable carbene. This was exemplified by the deprotonation of 1,3,4,5-tetramethylimidazolium chloride **37** to isolate 1,3,4,5-tetramethylimidazol-2-ylidene **38** (Scheme 41). As this was a sterically

unencumbered NHC, Arduengo suggested that stability here was mainly a result of the electronics of the ring.[34]



37 **38**

Scheme 41

Having developed a number of metal-NHC complexes, Herrmann noticed several similarities between the chemistry of NHCs and organophosphines (PR_3).[30,35] NHCs were deemed to be more akin to *P*-, *N*- or *O*-donating ligands than conventional carbenes, as the metal-carbon bond is significantly longer and is much more chemically and thermally stable. However, when compared to phosphines, NHCs were determined to have higher dissociation energies. They were described as strong two-electron donors with negligible π-backbonding. Hermann suggested that their high steric bulk would also stabilise the intermediates in catalytic cycles.[30,35]

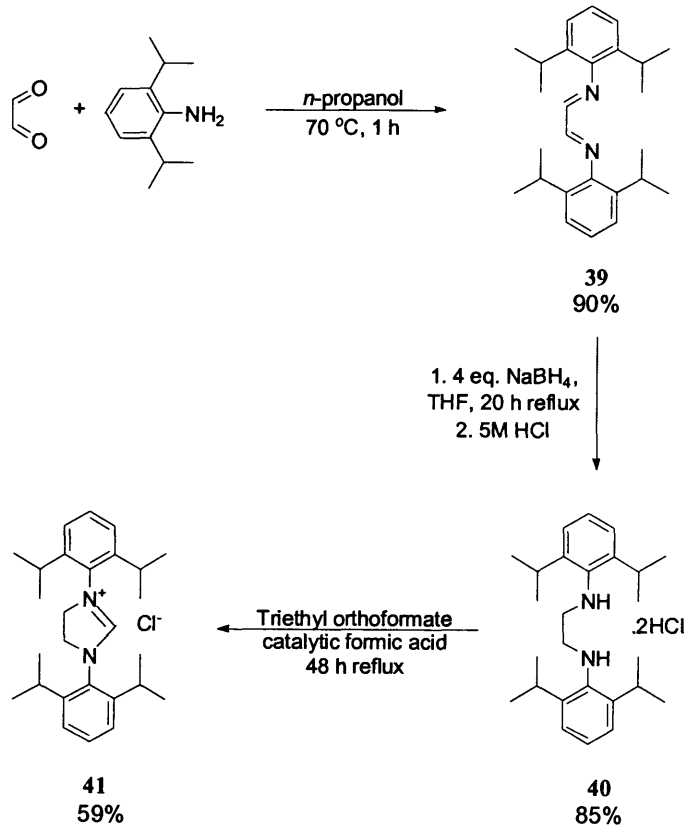
Accordingly, Hermann postulated that it would be possible to use NHCs as ancillary ligands (i.e. spectator ligands) in those transition metal-catalysed reactions that had traditionally utilised phosphines.[35] This observation helped to stimulate an interest into the preparation of transition metal-NHC complexes as potential replacements for the transition metal-phosphine complexes traditionally used as catalysts.

Due to their favourable stereoelectronics, as exemplified by **36** and **38**,[33,34] imidazol-2-ylidenes and 4,5-dihydroimidazol-2-ylidenes in particular have received a great deal of attention as suitable types of NHCs that can act as spectator ligands in palladium

chemistry (See section 1.3) and hence have been examined as part of this study in amine arylation (*vide infra*). Consequently, key examples of their preparation are described herein.

1.2.3. Key Examples for the Preparation of Imidazol-2-ylidenes and 4,5-Dihydroimidazol-2-ylidenes

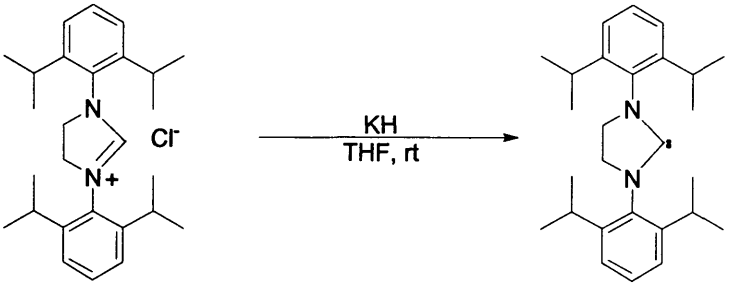
A superb procedure for the preparation of 4,5-dihydroimidazol-2-ylidenes was described by Arduengo in 1999. This convenient methodology allowed the synthesis of the imidazolinium salts 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr.HCl) and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (SIMes.HCl) in only three steps.[36]



Scheme 42

For example, SIPr.HCl was accessed *via* the formation of the diimine **39** from glyoxal and 2,6-diisopropylaniline. This was followed by reduction with sodium borohydride to furnish the amine, which was isolated as the hydrochloride salt **40** upon treatment with concentrated hydrochloric acid. Finally, reflux in an excess of triethyl orthoformate with catalytic formic acid yielded the imidazolinium salt **41** (Scheme 42).[36]

Arduengo also outlined how it was possible to deprotonate the imidazolium salts with sodium hydride to afford the desired carbenes: deprotonation of SIPr.HCl **41** gave the carbene 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) **42** (Scheme 43).[36]



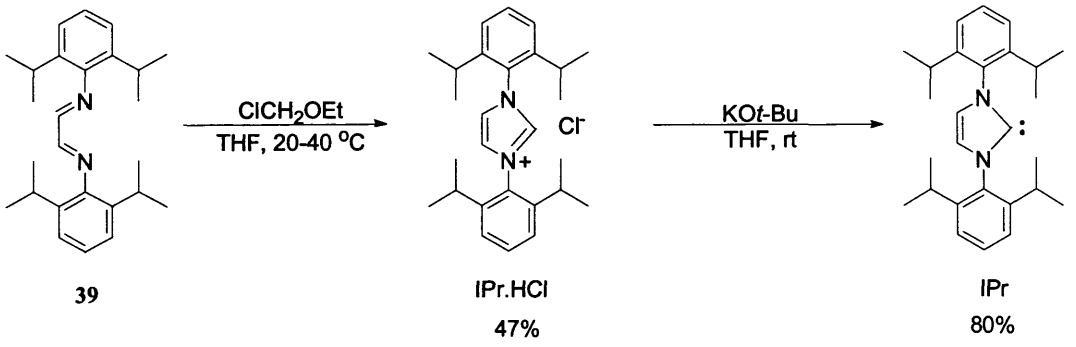
41
SIPr.HCl

42
SIPr
42%

Scheme 43

Arduengo additionally demonstrated the synthesis of the analogous imidazol-2-ylidenes. For instance, the unsaturated 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr.HCl) was prepared by reaction of **39** with chloromethylethyl ether (Scheme 44). Despite only a moderate yield, the imidazolium salt was obtained with sufficient purity to allow formation of the carbene 1,3-bis-(2,6-

diisopropylphenyl)imidazol-2-ylidene (IPr) *via* deprotonation with potassium hydride (Scheme 44).[36]

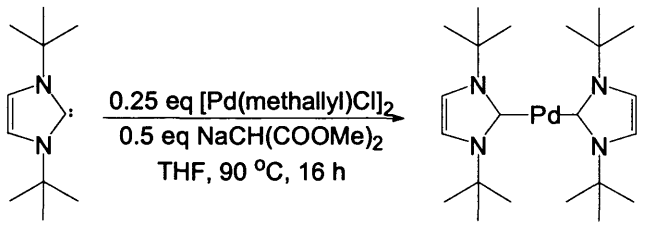


39 IPr.HCl 47% IPr 80%

Scheme 44

1.2.4. Key Examples of Palladium Complexes of Imidazol-2-ylidenes and 4,5-Dihydroimidazol-2-ylidenes

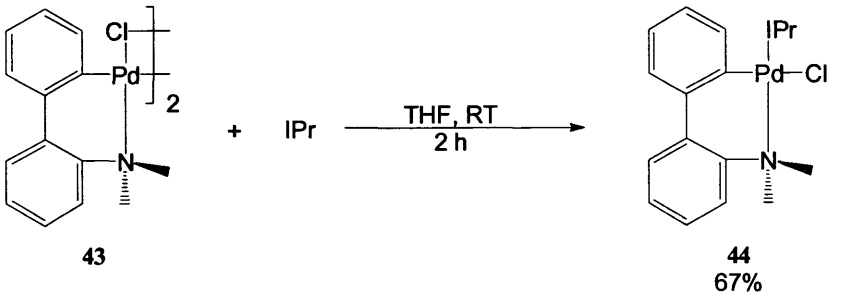
In some cases, Pd-NHC complexes may be formed through the reaction of an isolated carbene with a suitable palladium source. For instance, Caddick and Cloke demonstrated how the addition of sodium dimethylmalonate to the $[Pd(methallyl)Cl]_2$ dimer in the presence of the It-Bu carbene would afford the biscarbene palladium(0) complex $Pd(It\text{-}Bu)_2$ in 60% yield (Scheme 45).[37]



It-Bu $Pd(It\text{-}Bu)_2$ 60%

Scheme 45

In another example, the NHC-palladacycle **44** was prepared by Nolan in 67% yield *via* direct reaction with the IPr carbene with the dimeric **43** in THF at room temperature for 2 h (Scheme 46).[38]

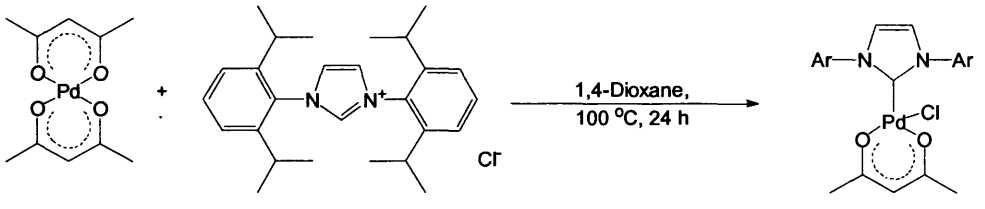


43 **44** 67%

Scheme 46

However, although it may be preferable to first isolate the NHC, it may not always be practical or possible, as this can require specialist equipment, such as an inert atmosphere glovebox. As an alternative, palladium complexes with imidazol-2-ylidenes and 4,5-dihydroimidazol-2-ylidenes are often isolated *via* the reaction of a palladium source with an imidazolium salt precursor.[39]

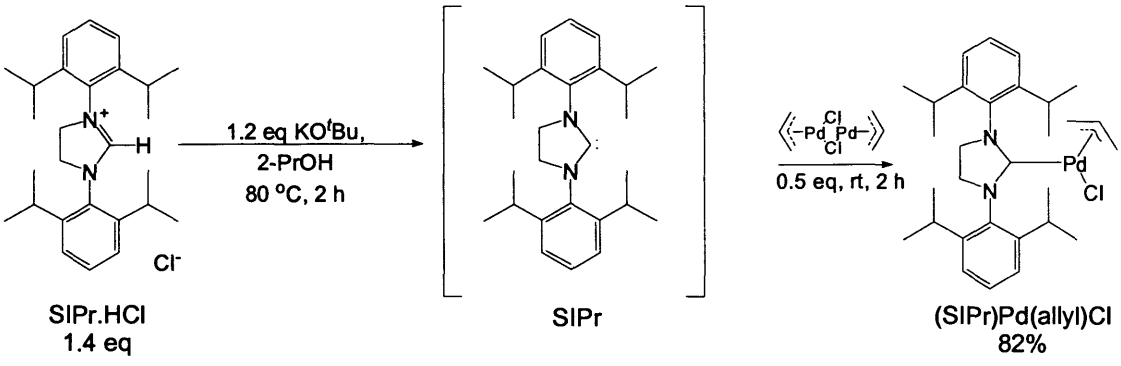
For example, a particularly facile synthesis for the active (IPr)Pd(acac)Cl catalyst was reported by Nolan in 2006.[40] The direct reaction of the commercially-available $Pd(acac)_2$ with an excess of IPr.HCl afforded the desired complex in near quantitative yield upon reflux in 1,4-dioxane for 24 h (Scheme 47).



IPr.HCl (IPr)Pd(acac)Cl 95%

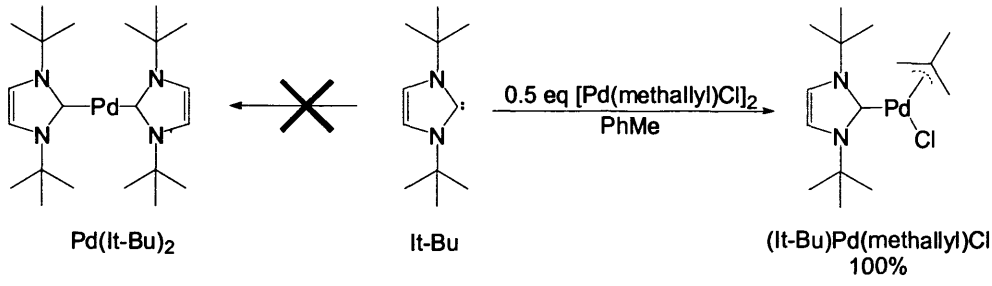
Scheme 47

(NHC)Pd(R-allyl)Cl complexes have also received considerable attention due to their activity in coupling reactions.[41] Nolan reported a large-scale one-pot procedure for the preparation of (NHC)Pd(allyl)Cl complexes through *in situ* deprotonation of SIPr.HCl or IPr.HCl followed by the addition of $[Pd(allyl)Cl]_2$.[42] This reaction was actually robust enough to be performed without the need for a dry solvent, as Nolan was able to utilise technical grade *iso*-propanol to successfully perform the reaction (Scheme 48).



Scheme 48

Interestingly though, the first (NHC)Pd(R-allyl)Cl complex was formed from an isolated carbene.[37] While examining a range of conditions for the preparation of Pd(It-Bu)$_2$ (*vide supra*) Caddick and Cloke isolated (It-Bu)Pd(methallyl)Cl under neutral conditions in toluene (Scheme 49). Several (NHC)Pd(R-allyl)Cl complexes have also been prepared by Nolan using similar techniques.[41]

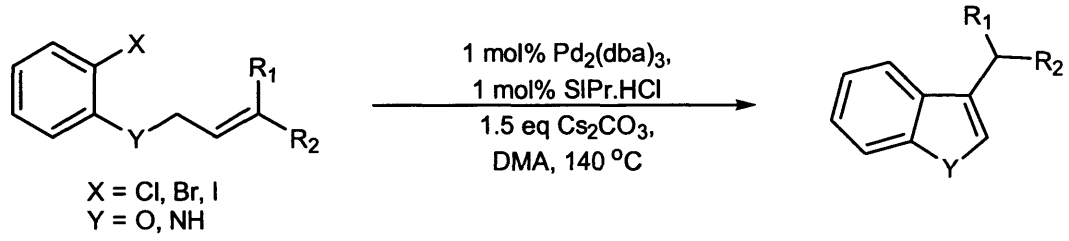


Scheme 49

1.2.5. Applications of Pd-NHC Catalysts in Cross Coupling Reactions

Although imidazol-2-ylidenes and 4,5-dihydroimidazol-2-ylidenes have been widely used as ancillary ligands in palladium-catalysed amine arylation (see section 1.3), they have also been utilised in a range of C-C bond forming reactions.

In one key publication, Caddick described the intramolecular Heck reaction of aryl halides with pendant olefin chains using a palladium(0) source with the imidazolium salt SIPr.HCl (Scheme 50).[9]



Scheme 50

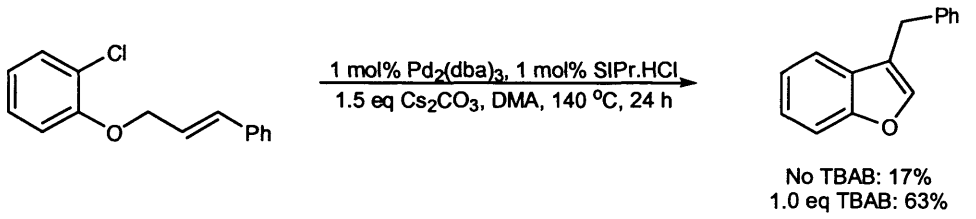
Aryl iodides were found to undergo high-yielding and rapid reactions, with no rearrangement or deallylation of the substrate being observed. Aryl bromides also afforded the desired products albeit with slightly slower reaction times and lower yields.[9]

Table 4: Intramolecular Heck reactions of 2-halophenyl cinnamyl ethers (Scheme 50; Y = O, R_1 = H, R_2 = Ph)

Entry	X	Additive	Yield/%
1	I	-	75
2	Br	-	50
3	Cl	-	-
4	Cl	TBAB[a]	63

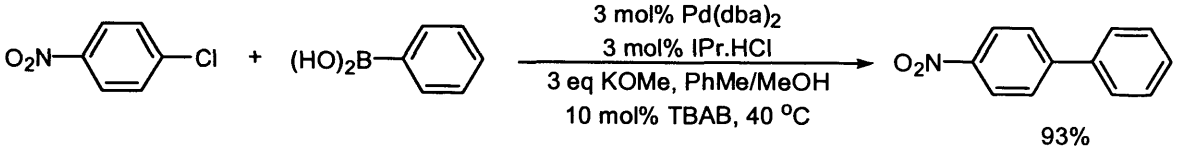
Conditions: 1 mol% $Pd_2(dba)_3$, 1 mol% SIPr.HCl, 1.5 eq Cs_2CO_3, DMA, 140 °C, 24 h. [a]1.0 eq of TBAB.

Aryl chlorides were significantly less reactive, either affording poor yields or failing to react altogether (Table 4). However, Caddick demonstrated how the addition of tetra-*n*-alkylammonium salts dramatically improved the yields with aryl chlorides to as high as 50–70%. This effect was due to the tetra-*n*-alkylammonium salts acting as a phase-transfer catalyst to increase the solubility of the preferred inorganic base cesium carbonate in the organic solvent DMA (Table 4, Scheme 51).[9]



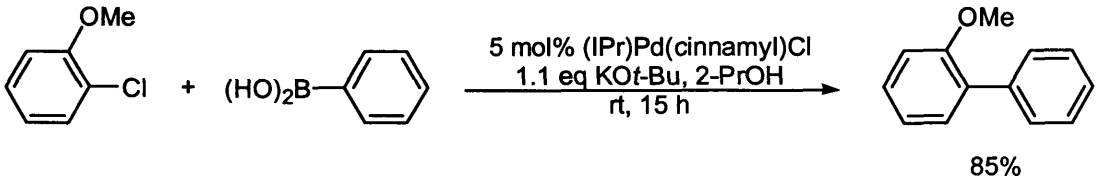
Scheme 51

Several protocols have also been described for Suzuki-Miyaura couplings of aryl halides. In one example, Caddick and Cloke were able to carry out reactions of a range of aryl chlorides at only 40 °C with a palladium(0) source and the imidazolium salt IPr.HCl (Scheme 52).[43]



Scheme 52

Reactions have also been carried out using isolated Pd-NHC complexes. Nolan demonstrated in 2006 that the high-yielding room temperature reactions of a number of aryl chlorides and boronic acids were possible using the (IPr)Pd(cinnamyl)Cl complex (Scheme 53).[41]



Scheme 53

1.2.6. Summary

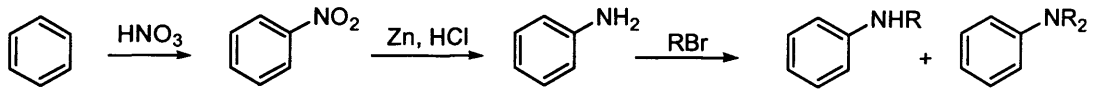
An abundance of transition metal complexes containing NHC ligands have been developed since the work of Ofele and Wanzlick.[31,32] Following the convenient syntheses for imidazol-2-ylidenes and 4,5-dihydroimidazol-2-ylidenes by Arduengo, a number of active Pd-NHC catalysts have been prepared and their application in amine arylation is discussed in the following section.

More advanced complexes have seen increases in substrate scope, yield and turnover in addition to vast reductions in reaction times. Hence, new Pd-NHC complexes and reaction protocols have been examined as part of this study with the aim of further advancing beyond the *status quo*.

1.3. The Buchwald-Hartwig Reaction: Pd-Catalysed Amine Arylation

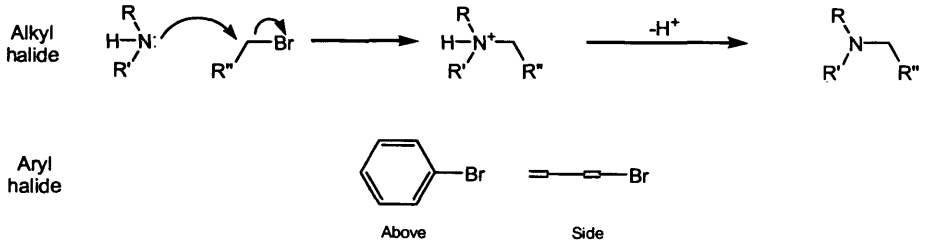
1.3.1. Early Developments in Amine Arylation

The aniline moiety is of particular importance in modern organic chemistry due to its regular occurrence in biologically active molecules.[44] Its synthesis has traditionally been carried out in several steps, specifically utilising the nitration of an aromatic ring *via* electrophilic substitution, followed by reduction to the primary aniline and the subsequent nucleophilic substitution of an alkyl halide (Scheme 54).[45]



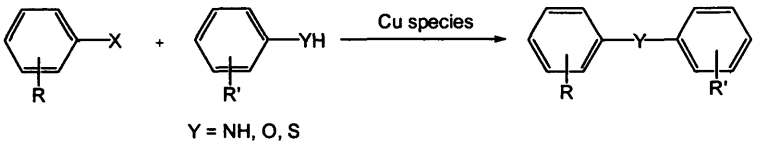
Scheme 54

An alternative means of obtaining substituted anilines may be to use a transition metal to mediate the reaction between an aryl halide (or triflate) and an amine. The transition metal is necessary in these cases as the planar aromatic ring prevents the nucleophilic attack that is possible with alkyl halide substrates (Scheme 55).[46]



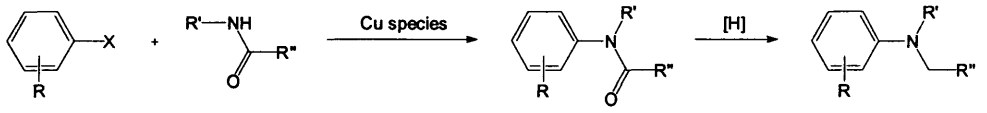
Scheme 55

First reported in 1903, the Ullmann condensation has often been used to mediate C-N bond formation in the reactions of aryl halides and anilines (Scheme 56).[47]



Scheme 56

In 1906, the Goldberg modification of the Ullmann reaction was first reported. This improved version of the reaction allowed coupling with amides as well as anilines, increasing the scope of the reaction (Scheme 57).[48]

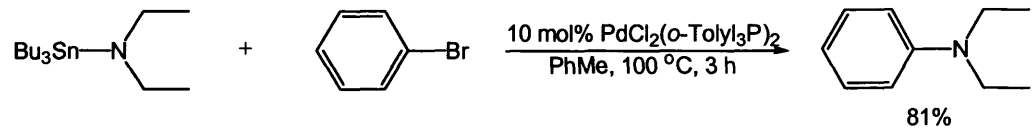


Scheme 57

However, a number of disadvantages were associated with the Ullmann condensation, including requirements such as high temperatures, a strong base and a polar solvent (such as the toxic HMPA). These demands would often lead to low yields and the attack of fragile functional groups.[47,48] Additionally, the copper metal or copper reagents employed in the reaction would often be required in stoichiometric amounts, increasing the cost of the reaction. Although a number of recent developments have been made to improve this transformation, particularly with the use of sub-stoichiometric levels of copper,[49] significant advances in the preparation of substituted anilines have arisen instead through the use of palladium catalysis.

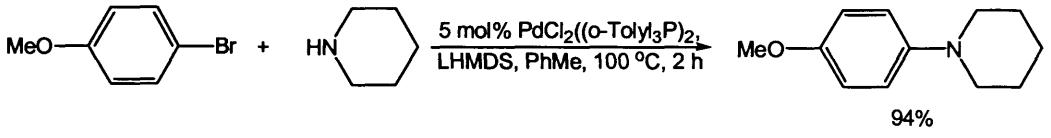
1.3.2. The Buchwald-Hartwig Amine Arylation

One of the earliest reports of aryl halide amination under palladium catalysis was made by Migita in 1983. Here it was shown to be possible to couple an aryl bromide with a tin amide, in a process analogous to the Stille reaction (Scheme 58).[50]



Scheme 58

Realising the potential of this reaction, Hartwig and Buchwald independently re-examined Migita's work to enable the *in situ* generation of the tin amide.[51,52] In 1995 they both reported that it was possible to replace the tin amide with a free amine if the reaction was carried out in the presence of a strong base (Scheme 59).[53,54]

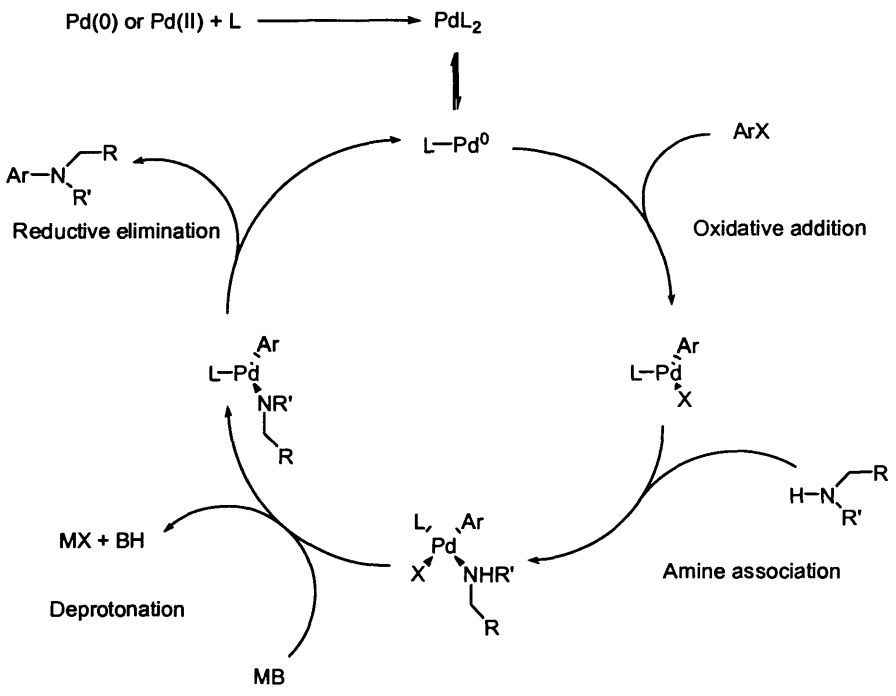


Scheme 59

These key findings have since been followed by a plethora of reports concerning this reaction from academia and industry, with a number of innovations described in the decade following its genesis. The palladium-catalysed amine arylation has come to be known as the "Buchwald-Hartwig" reaction.

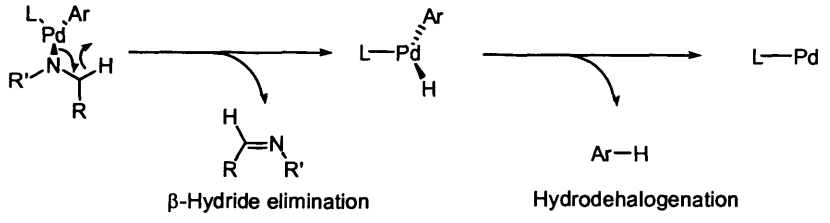
1.3.3. Mechanism of Buchwald-Hartwig Amine Arylation

The proposed mechanism of the Buchwald-Hartwig reaction is similar to other Pd-catalysed reactions:[53,55] after the generation of what is believed to be a mono-ligated active species,[56,57] oxidative addition of the halide occurs at the Pd centre, followed by association of the amine (the latter two steps are regarded as rate determining steps). After deprotonation of the amine, reductive elimination occurs to afford the aniline product and regenerate the catalyst (Scheme 60).[53,54]



Scheme 60

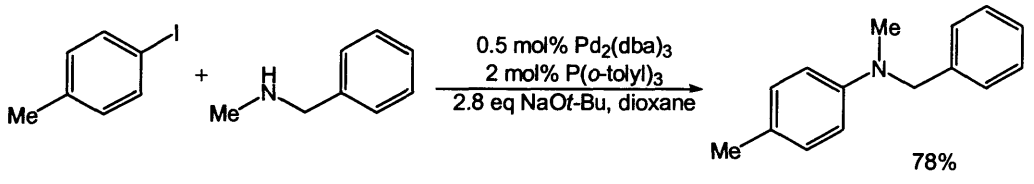
The active species is stabilised by a carefully-selected highly electron-donating and bulky ligand (*vide infra*), which then allows oxidative addition to occur. The oxidative addition step is believed to proceed through a concerted rather than radical process. The undesired side reaction of β-hydride elimination may also occur in competition with reductive elimination, affording the imine analogue of the amine substrate. This process also leads on to hydrodehalogenation of the aryl halide (Scheme 61). However, larger ligands promote reductive elimination over this process.[53-57]



Scheme 61

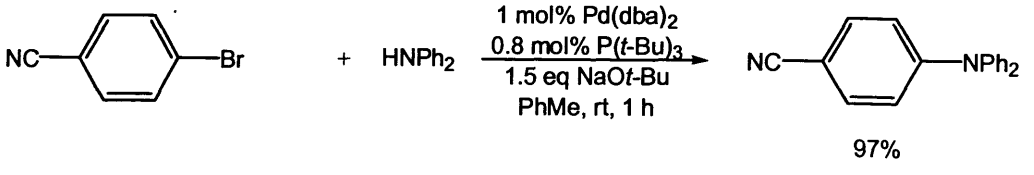
1.3.4. Key Advances in the Buchwald-Hartwig Amine Arylation

Improved catalysts have built upon the initial findings of Buchwald and Hartwig by allowing the coupling of a wider range of substrates and the use of milder basic conditions. In an early example, Buchwald reported the coupling of aryl iodides with secondary alkyl amines or secondary anilines using a palladium(0) source and P(*o*-tolyl)$_3$ (where the active catalyst was formed *in situ*) at 100 °C with sodium *tert*-butoxide. (Scheme 62).[58] Although the alkoxide base was still relatively strong, it was nonetheless milder than the lithium hexamethydisilazide (LHMDS) used in the initial reports.[53,54]



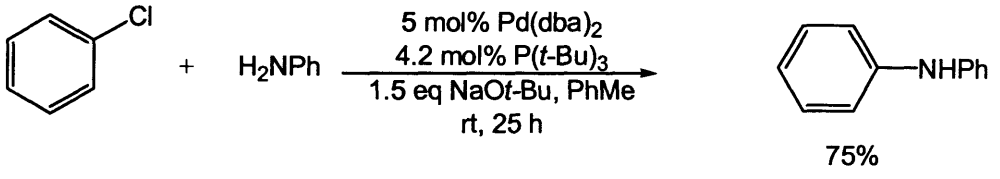
Scheme 62

The versatility of the reaction increased significantly, mainly as a result of the employment of alkyl phosphine ligands and the extra activity afforded by their high electron donor ability and larger steric bulk. The remarkable rate at which further advances were reported may be illustrated by the fact that in 1999, only four years after the first reported reactions,[53,54] Hartwig was able to describe room temperature reactions of aryl bromides with various amines using a system of Pd(0)/(P*t*-Bu$_3$) in near-quantitative yields (Scheme 63).[59]



Scheme 63

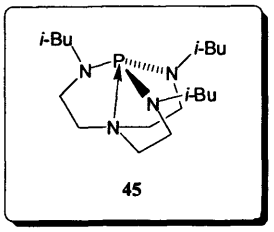
With the same protocol, Hartwig showed that unactivated aryl chlorides would react at 70 °C with 1-5 mol% catalyst in high yields; additionally, activated aryl chlorides were reported to react at room temperature.[59] With higher catalytic loading, the unreactive $PhNH_2$ was found to react with chlorobenzene at room temperature in 25 h (Scheme 64).[59] The highly-activating P(*t*-Bu)$_3$ ligand also enabled reactions with different molecules containing the N-H moiety, including indoles and carbamates.[59]

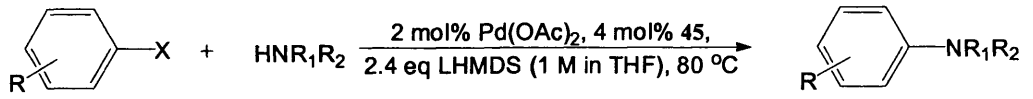


Scheme 64

However, one drawback with many protocols was their incompatibility with a range of sensitive functional groups, due to their reliance on strong alkoxide bases.[60] Milder bases (e.g. Cs_2CO_3) which would not attack these functional groups were also often too mild to efficiently perform the reaction. Even aryl iodides would only react at temperatures in excess of 100 °C under such mild conditions.[61]

Subsequent reports endeavoured to address this issue. For example, in 2004 Verkade outlined the use of a palladium source with the proazaphosphatrane ligand P(*i*-Bu$NCH_2CH_2)_3N$ **45**. This allowed the reaction of aryl halides possessing a phenol, alcohol, acetaniline, amide or enolisable ketone moiety with LHMDS as base (Scheme 65).[62] Verkade offered a practical reaction procedure as the LHMDS was used as a commercially available 1 M solution in THF in preference of the solid LHMDS which required an inert atomsphere.[62]

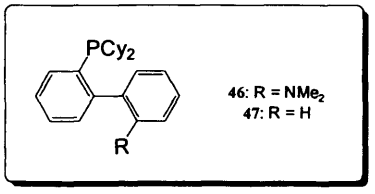


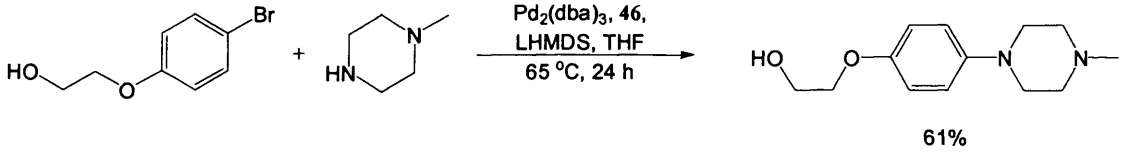


R = OH, CH_2CH_2OH, NHAc, COMe, $CONH_2$
NHR_1R_2 = primary or secondary amines

Scheme 65

Buchwald also noted the functional group compatibility of LHMDS in place of alkoxide bases in 2002, using the bulky electron-rich phosphine ligands **46** and **47** (Scheme 66), although the compatibility that was observed was not as encompassing as that achieved with **45**.[63]

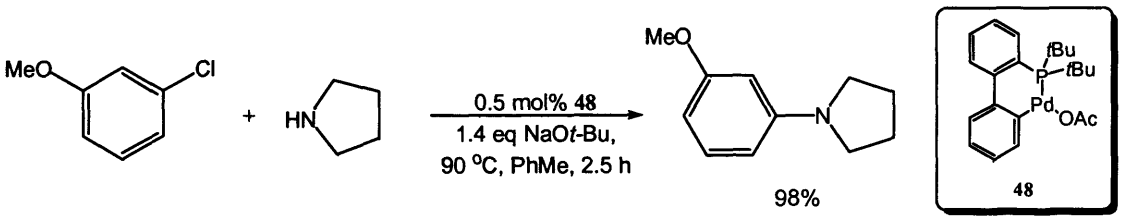




61%

Scheme 66

Current advances are now often concerned with improving the practicality of the reaction, particularly with respect to removing the need for a glovebox. For example, Buchwald recounted the use of a one-component palladacycle catalyst **48**, which was developed from **46** and **47**. **48** was reported to be simple to prepare, with the added benefit of being air- and moisture-stable upon isolation (Scheme 67).[64]



Scheme 67

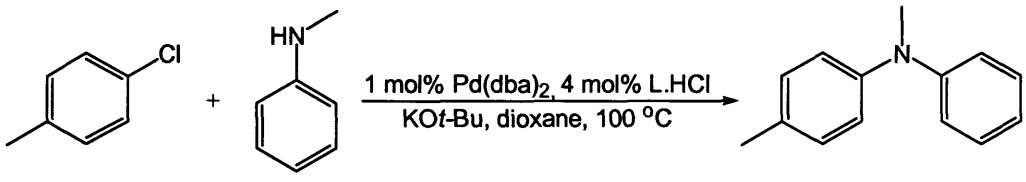
1.3.5. *N*-Heterocyclic Carbenes (NHCs) as Ancillary Ligands in Palladium-Catalysed Amine Arylation

As exemplified above, the majority of protocols for the Buchwald-Hartwig reaction throughout the 1990s made use of phosphine (PR_3) ligands,[65,66] despite the drawbacks associated with phosphines and palladium-phosphine complexes.[4] Aryl phosphines, like triphenylphosphine, are reasonably facile to handle, but are limited in their activity. Conversely, the newer, more hindered and electron rich alkyl phosphines (e.g. tri-*tert*-butylphosphine) are highly active in comparison, but are particularly sensitive to air and moisture, meaning a glovebox is mandatory to prevent oxidation.[4,66] Additionally, alkyl phosphines are sometimes liquids[67] and are often accompanied by highly pungent odours which may make them difficult to handle.

Recently, substantial research has been undertaken into *N*-heterocyclic carbene (NHC) ligands (as used by Grubbs in his work on ruthenium catalysis)[68] as potential phosphine replacements. A number of both unsaturated and saturated NHCs of varying ring size have been developed in recent years, with their excellent electron donor ability resulting in strong Pd-NHC bonds that often translate to high levels of catalytic activity, with examples in Heck and Suzuki reactions (see section 1.2). Pd-NHC catalysts are either used as isolated complexes or are generated *via in situ*

deprotonation of a stable imidazolium salt in the presence of a Pd source (See section 1.2).

In 1999 Nolan reported the use of a palladium(0) source and an imidazolium salt as catalyst precursors in the amination of aryl chlorides.[69] Optimisation with several different imidazolium salts showed that the bulky 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr.HCl) offered the highest conversion rate in this system (Scheme 68; Table 5, Entry 5).[69]



Scheme 68

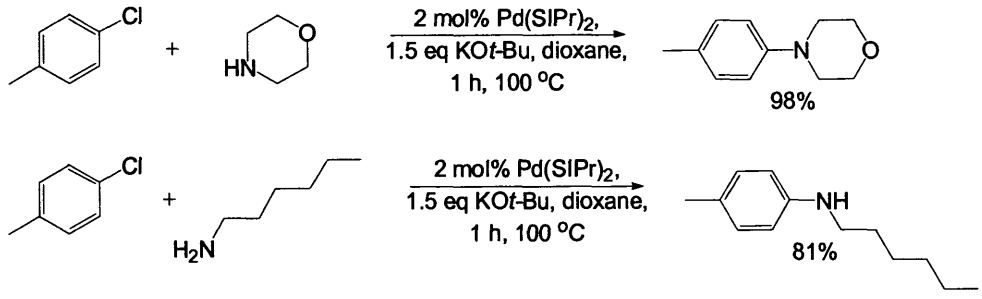
Table 5: Buchwald-Hartwig amination of 4-chlorotoluene with *N*-methylaniline with palladium(0)/ imidazolium chlorides.[70]

Entry	Ligand (L)	Time (h)	Yield (%)[a]
1	None	3	0
2	ITol	3	<5
3	IXy	3	11
4	IMes	3	22
5	IPr	3	98

[a]Isolated yields averaged over two runs.

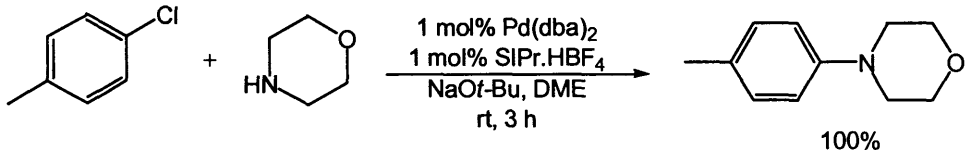
Aryl bromides and iodides were found to react at room temperature, whereas aryl chlorides required temperatures of 100 °C.[69] Coupling was performed on a variety of primary and secondary amines using a 1:2 Pd/ligand ratio, as it was thought that this would match the Pd/ligand ratio should the biscarbene complex $Pd(IPr)_2$ be formed *in situ en route* to the active species $[(IPr)Pd^0]$.[69]

Using the biscarbene complex $Pd(SIPr)_2$, Caddick and Cloke demonstrated that the near-quantitative reactions of selected aryl chlorides were possible within an hour. With an excess of amine, the coupling of 4-chlorotoluene and the primary amine *n*-hexylamine was even possible, albeit in a lower yield. Reactions were found not to proceed at room temperature (Scheme 69).[70]



Scheme 69

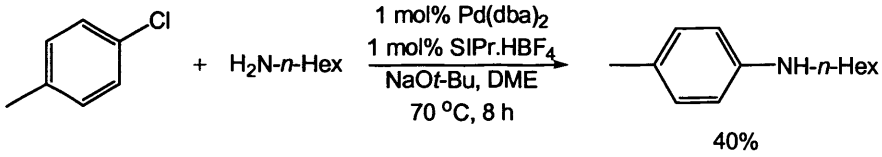
However, Hartwig reported the room temperature amination of aryl chlorides using a similar *in situ* protocol with only 1 mol% of a Pd(0) source and the imidazolinium salt $SIPr.HBF_4$ (Scheme 70).[56] It was shown that the best results were achieved with cyclic secondary amines, with most reactions complete within five hours in quantitative or near-quantitative yields.[56]



Scheme 70

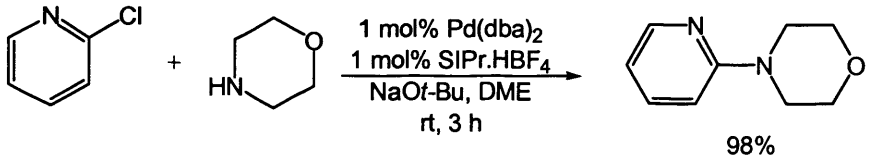
Nevertheless, sterically-hindered secondary amines such as dicyclohexylamine failed to react at all, even at higher catalyst loadings (2 mol%) or elevated temperatures (70 °C). Additionally, it was found that acyclic secondary amines and unhindered anilines required 2 mol% of palladium to improve their activity in comparison to

secondary cyclic amines. Reactions with primary alkylamines required higher temperatures (70 °C) and afforded significant amounts of hydrodehalogenation to give toluene through reductive elimination (Scheme 71). It was asserted that Nolan's use of an unsaturated ligand would be more suitable for these substrates due to the increased electron density (*vide supra*).[69] Again, in all reactions, milder bases including Cs_2CO_3 and K_3PO_4 were found to be ineffective.[56]



Scheme 71

Nevertheless, the coupling of chloropyridines was found to be more facile under Pd-NHC catalysis than under Pd-phosphine catalysis, as in the latter there is competition between the pyridyl lone pair and the phosphine for coordination to palladium.[71] Hartwig showed that the strong Pd-NHC bonds prevented this competitive inhibition (Scheme 72).[70]

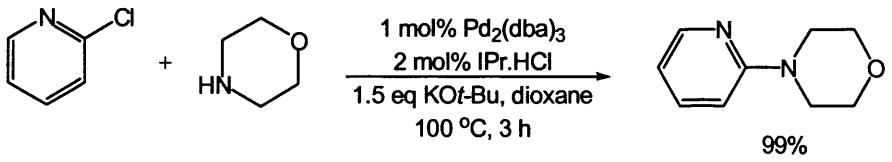


Scheme 72

In contrast to Nolan's earlier work,[69] a 1:1 Pd/ligand ratio was found to afford the fastest rates for conversion; it was believed that this gave the best conditions to promote the formation of the active mono-ligated species [(SIPr)Pd(0)]. Hartwig also postulated that the rate of reaction was determined by the amine and not the aryl

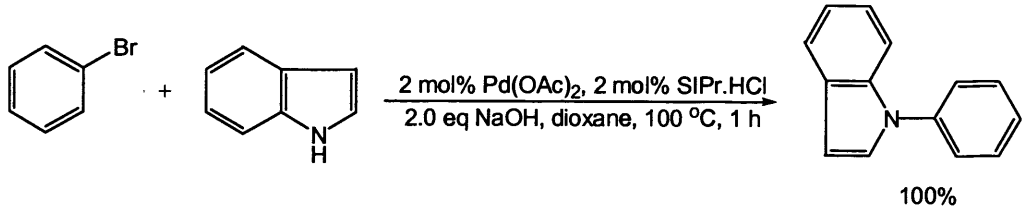
chloride.[56] This was a logical hypothesis, as different amines reacted at different rates with identical halides.

In 2001, Nolan increased the substrate scope of the reaction, by attempting to build upon Hartwig's findings with 2-chloropyridine. However, it was found that the coupling of 2-chloropyridine and morpholine required heating at 100 °C in order to proceed (Scheme 73).[72] This may be attributed to Nolan's use of IPr.HCl in place of SIPr.HCl, apparently showing the benefit of the more electron-rich saturated ligand.



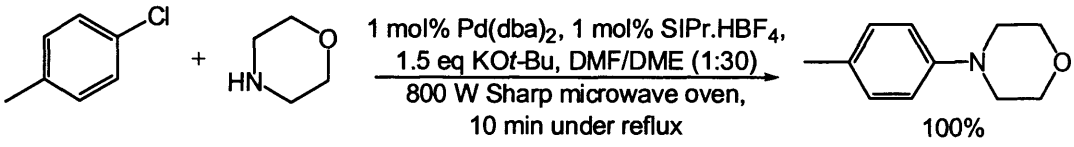
Scheme 73

However, the *N*-arylation of indole was found not to proceed under these conditions. The N-H moiety in indole is less reactive than those found in alkyl amines, as the lone pair of the nitrogen atom is less available due to the delocalisation of electrons in the aromatic ring. This makes indole significantly less nucleophilic and hence less reactive in Buchwald-Hartwig reactions. Nolan preferred SIPr.HCl in this reaction, using sodium hydroxide to generate the free carbene (Scheme 74).[72] In agreement with Hartwig's findings, Nolan also reported an optimum Pd to ligand ratio of 1:1.[70,72]



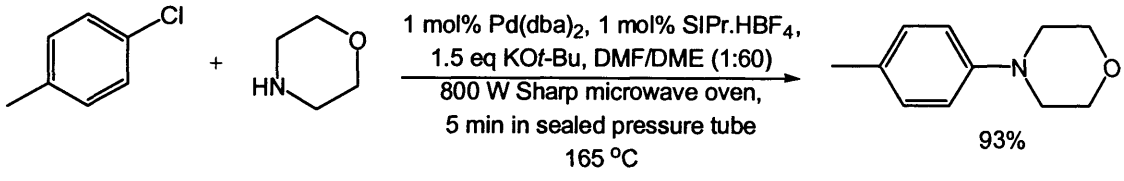
Scheme 74

Approaching the reaction from a different perspective, Caddick and Cloke concentrated on improving reaction times and reliability on simple substrates, with the aim of applying amine arylation to combinatorial chemistry. The coupling of aryl chlorides was facilitated with heating at high temperatures using an 800 W domestic microwave oven fitted with a reflux condenser. Under these conditions, amine arylation was possible in 5-10 min in moderate to high yields (Scheme 75).[73]



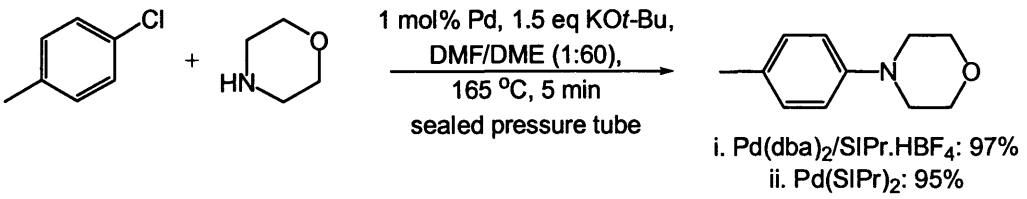
Scheme 75

The microwave protocol was enhanced with the use of sealed tubes in an 800 W domestic microwave oven under similar conditions, with all reactions complete in under 5 min (Scheme 76). Investigations showed that these rates could be replicated with thermal heating at 165 °C. However, this clearly lacked the practicality of the microwave setup.[73]



Scheme 76

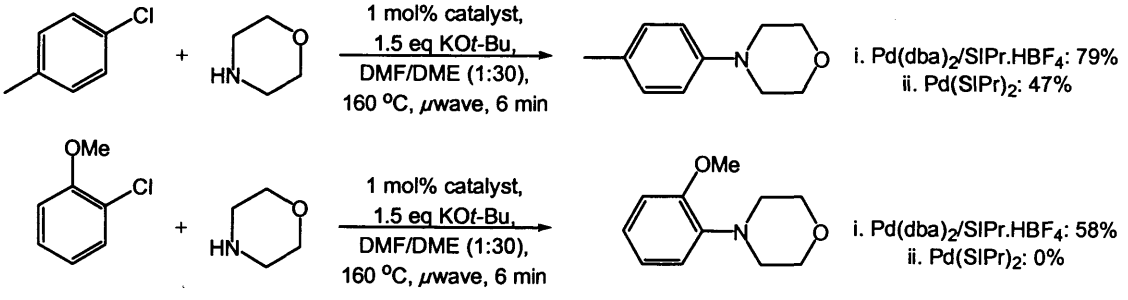
Under thermal conditions, there was found to be little difference in terms of rate between the *in situ* protocol with $SIPr.HBF_4$ or that with the isolated complex $Pd(SIPr)_2$ (Scheme 77). Nevertheless, the *in situ* protocol was considered advantageous due to its practicality.[73]



Scheme 77

Further investigations showed that the use of a commercially-available microwave reactor, specifically designed for organic synthesis, was significantly better than the domestic microwave oven, both in terms of safety and reaction yield. With this instrument, more selectivity was possible when selecting the temperature, pressure and power at which heating would occur.[73]

In the commercial laboratory microwave reactor, the *in situ* protocol was found to be more effective than that with the isolated complex $Pd(SIPr)_2$. This was possibly as a result of the relative stabilities of the complexes under heating (Scheme 78), but another consideration was the possibility of more facile access to the active species [(NHC)Pd(0)]. Interestingly, it was also noted that there was no difference observed in the rate or yields of the reactions when using or a chloride or tetrafluoroborate counterion on the imidazolium salts.[73]

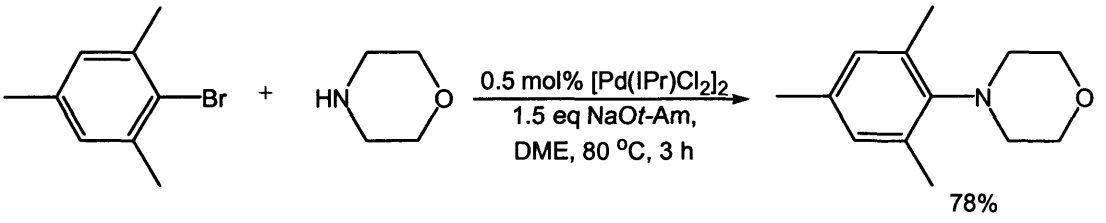


Scheme 78

1.3.6 Examples of Advanced *N*-Heterocyclic Carbenes (NHCs) as Ancillary Ligands in Palladium-Catalysed Amine Arylation

Although significant advances have been made in the Buchwald-Hartwig reaction with imidazolium salts, it has become apparent that they may not offer the key to rapid room temperature protocols for all substrates. Therefore, efforts are increasingly concentrating on developing novel isolable Pd-NHC complexes that will improve upon the homoleptic biscarbene complexes such as $Pd(SIPr)_2$. These complexes are being specifically designed with properties that will enhance their reliability and activity in coupling reactions. The latter is being achieved by developing complexes that offer more facile access to the active species [(NHC)Pd^0].

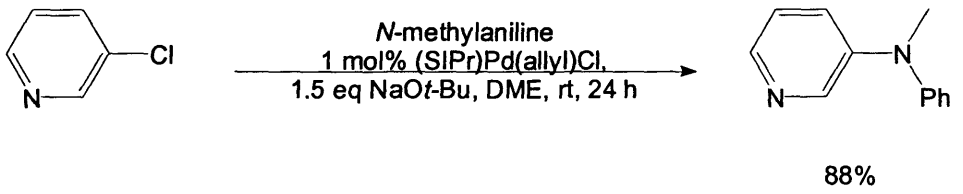
For example, Nolan described how when using $[Pd(IPr)Cl_2]_2$ that activated aryl bromides and chlorides would undergo amination within minutes, with deactivated or hindered aryl bromides and chlorides reacting within 3 h (Scheme 79).[75] This protocol was particularly stable to air, allowing reactions to be performed without the need for dried solvents or distilled substrates, with little effect on reaction rate or yield.[74]



Scheme 79

Further improvements in the efficiency of the Buchwald-Hartwig reaction have come through the development of the (NHC)Pd(R-allyl)Cl class of complexes. These were first prepared by Caddick and Cloke in 2000 when (It-Bu)Pd(methallyl)Cl was prepared as an intermediate in the synthesis of the biscarbene complex

$Pd(It\text{-}Bu)_2$ (see section 1.2).[37] In 2002, Nolan showed that these complexes could also be utilised in cross coupling reactions, as (SIPr)Pd(allyl)Cl was shown to successfully mediate the amination of several aryl chlorides (Scheme 80).[75]



Scheme 80

In 2004, Nolan reported a comparison of (NHC)Pd(allyl)Cl catalysts possessing different NHC ligands. In the reaction of 4-chlorotoluene and morpholine, most complexes tested resulted in quantitative or near quantitative yields. However, the fastest reaction rates were achieved with (IPr)Pd(allyl)Cl and (SIPr)Pd(allyl)Cl (Table 6, Entries 7-8).[76]

However, when performed at room temperature, (SIPr)Pd(allyl)Cl was shown to be significantly faster at mediating the coupling. The case for making SIPr the ligand of choice in amine arylation was further strengthened here, as (SIPr)Pd(allyl)Cl afforded 100% conversion compared to the 95% conversion afforded by (IPr)Pd(allyl)Cl (Table 6, Entries 9-10).[76]

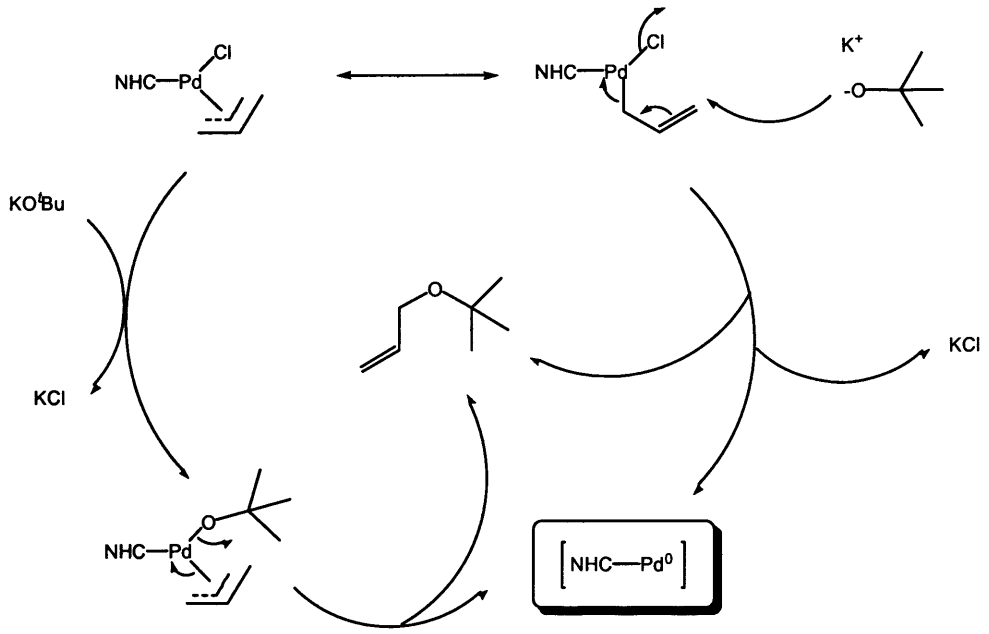
The activity of (NHC)Pd(allyl)Cl complexes appeared to stem from the fact that they would offer more facile access to the mono-ligated active catalytic species than imidazolium salt techniques, partly as this bond was already formed prior to reaction. Thus, activation would consist of reduction from Pd(II) to Pd(0) *via* the base-mediated removal of the Cl group and allyl scaffold. A mechanism for this activation

was proposed by Nolan for (NHC)Pd(allyl)Cl, with two different pathways, both of which would afford [(NHC)Pd(0)] (Scheme 81). One pathway was believed to occur through nucleophilic attack of the base on the allyl scaffold in a concerted fashion. The other pathway was proposed to consist firstly of replacement of the Cl at the metal centre with the alkoxide base, followed by reductive elimination.[76]

Table 6: Buchwald-Hartwig coupling of 4-chlorotoluene and morpholine with (NHC)Pd(allyl)Cl.[76]

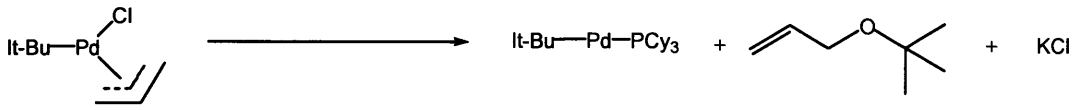
Entry	NHC	Temperature / °C	Time / h	GC Yield / %
1	ICy	80	-	-
2	*N,N'*-bis(1-*S,S*-pheny-lethylimidazol)-2-ylidene	80	-	-
3	IAd	80	2	100
4	It-Bu	80	3	99
5	IMes	80	2	100
6	SIMes	80	1.6	100
7	IPr	80	0.25	100
8	SIPr	80	0.25	100
9	IPr	rt	6	95
10	SIPr	rt	1.25	100

Conditions: 1 mmol 4-chlorotoluene, 1.2 eq morpholine, 1 mol% cat, 1.5 eq NaO*t*-Bu, 4 mL DME



Scheme 81

The formation of the active species was confirmed through an experiment where it was trapped through the addition of tricyclohexylphosphine to the complex (It-Bu)Pd(allyl)Cl. (It-Bu)Pd(PCy_3) was observed by Nolan in addition to the *tert*-butyl allyl ether and potassium chloride by-products (Scheme 82).[76]

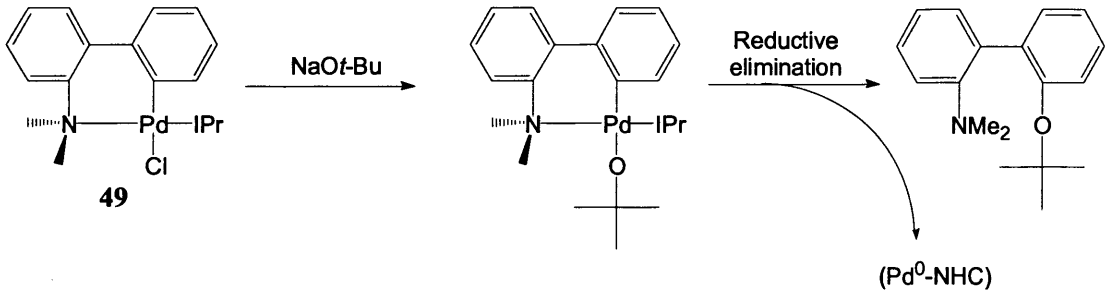


Scheme 82

As (NHC)Pd(R-allyl)Cl catalysts are isolated complexes, there is control over the Pd:ligand ratio, notwithstanding decomposition. This is an important benefit, as a 1:1 ratio is generally regarded to offer the fastest rate of reaction through its promotion of the mono-ligated active species.[76] Additionally, the complexes can be made without a glovebox or even the need for dry solvents.[42] Work by Sigman to prepare (NHC)Pd(allyl)Cl showed that these complexes are stable enough to be purified *via*

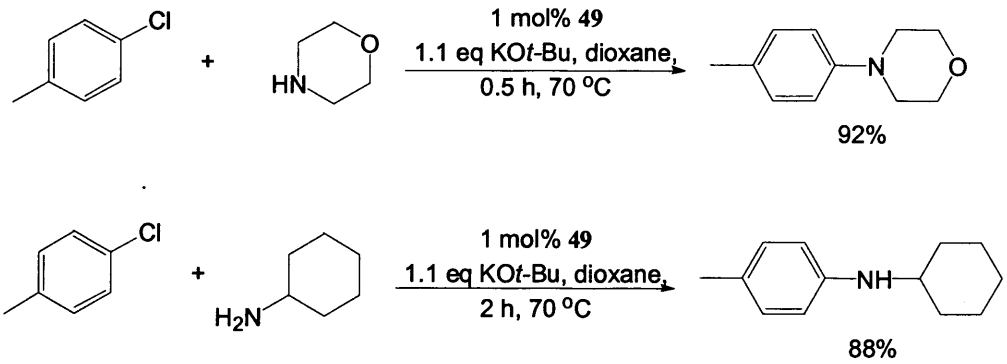
flash column chromatography with silica gel, and that once prepared, are indefinitely air- and moisture-stable.[77]

Following this success with the (NHC)Pd(allyl)Cl complex, Nolan showed that a similar mode of activation could be used to access the [(NHC)Pd(0)] active species from NHC-palladacycle dimers.[38] Based upon observations from spectroscopic analysis, Nolan hypothesised that activation of the palladacycle **49** would commence with attack of the butoxide base on the palladium centre to afford a palladium-alkoxide species. This would then undergo reductive elimination to afford the active species (Scheme 83).[38]



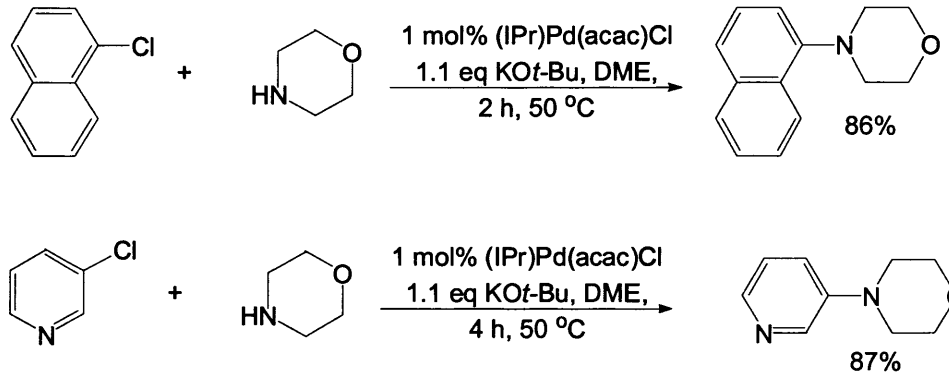
Scheme 83

49 was shown to increase activity in this reaction, as it mediated the coupling of a number of aryl chlorides and amines within two hours at 70 °C (Scheme 84).[38]



Scheme 84

In 2006, Nolan developed the complex (IPr)Pd(acac)Cl.[40] This was expected to mediate amine arylation in the same manner as (NHC)Pd(allyl)Cl. However, it was hoped that the acac scaffold would be removed more easily than allyl leading to more facile access to the active species. (IPr)Pd(acac)Cl was demonstrated to be more active than the previous complexes developed by Nolan, as efficient couplings were found to be possible at only 50 °C (Scheme 85).[40]



Scheme 85

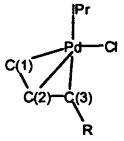
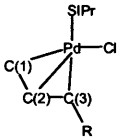
Despite the improvements made with these complexes, most amination reactions using isolated Pd-NHC complexes still required heating in order to mediate the reactions of aryl chlorides. Nolan concluded that activity could be bettered by increasing the lability of the group removed to afford the [(NHC)Pd(0)] active species. It was considered that substitution of the allyl scaffold in (NHC)Pd(allyl)Cl complexes would result in more facile activation.[41]

Substitution would in theory stabilise the complex by increasing the steric bulk about the Pd centre and by reducing the Pd-allyl electron back-bonding. Nolan conjectured that this would weaken the bonding between the allyl scaffold and the Pd centre, meaning that it would be more easily removed to afford the active species. Consequently, Nolan embarked upon a study of modified (NHC)Pd(R-

allyl)complexes. The bond lengths between the metal centre and the allyl scaffold were determined in several different complexes containing both the IPr and SIPr ancillary ligands as it was expected that the strength of the bonding would fall as bond length increased (Table 7).[41]

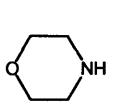
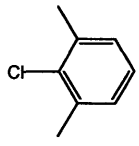
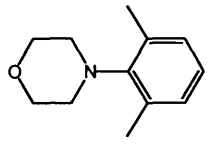
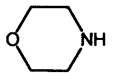
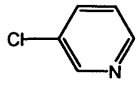
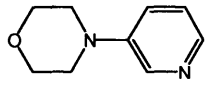
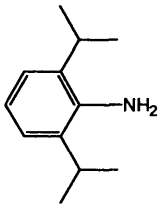
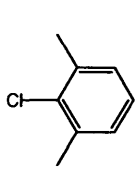
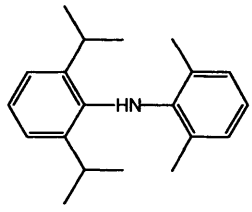
Examination of the IPr-bearing complexes indicated that whilst the Pd-C(1) distance was generally constant regardless of substitution, the Pd-C(3) distance became longer as terminal substitution on the allyl scaffold increased. Whilst terminal phenyl substitution was less electron donating than the methyl substitution found in the crotyl and prenyl-substituted complexes, elongation of the Pd-C(3) distance in (IPr)Pd(cinnamyl)Cl was found to be even greater than in (IPr)Pd(prenyl)Cl. Juxtaposition of (SIPr)Pd(allyl)Cl and (SIPr)Pd(cinnamyl)Cl also showed that terminal phenyl substitution increased the bond distances between the palladium centre and the bound carbon centres on the allyl scaffold.[41]

Table 7: Effects on Pd-C bond lengths in (NHC)Pd(R-allyl)Cl due to terminal substitution of the allyl scaffold (Å).[41]

IPr	Bond	(IPr)Pd(allyl)Cl	(IPr)Pd(crotyl)Cl	(IPr)Pd(prenyl)Cl	(IPr)Pd(cinnamyl)Cl
	Pd-C(1)	2.098(6)	2.147(18)	2.095(4)	2.082(9)
	Pd-C(2)	2.124(7)	2.122(18)	2.137(5)	2.136(10)
	Pd-C(3)	2.210(6)	2.209(16)	2.252(5)	2.284(9)
SIPr	**Bond**	**(SIPr)Pd(allyl)Cl**	**(SIPr)Pd(crotyl)Cl**	**(SIPr)Pd(prenyl)Cl**	**(SIPr)Pd(cinnamyl)Cl**
	Pd-C(1)	2.118(6)	-	-	2.136(10)
	Pd-C(2)	2.132(7)	-	-	2.137(8)
	Pd-C(3)	2.203(6)	-	-	2.279(10)

In order to determine the effects of bond length, these complexes were examined in amine arylation. Nolan's results, using carefully-selected challenging substrates, showed the significant effects of both the ancillary ligand (SIPr in place of IPr) and of increased terminal substitution on the allyl scaffold from allyl to cinnamyl (Table 8). As such, Nolan determined that (SIPr)Pd(cinnamyl)Cl was the preferred pre-catalyst for use in this reaction due to its ability to mediate room-temperature N-H arylation within minutes even on aryl chlorides.[41]

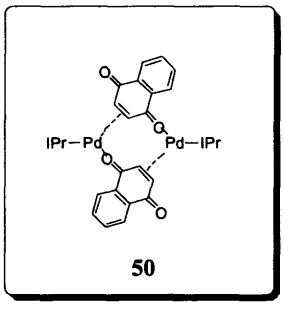
Table 8: Effects of the NHC ancillary ligand and substitution on the allyl scaffold in room temperature amine arylation.[41]

Amine	Halide	Product	Pre-catalyst	Time/h	GC conv/%
			(IPr)Pd(allyl)Cl	5	98
			(SIPr)Pd(allyl)Cl	2.5	99
			(IPr)Pd(cinnamyl)Cl	2	100
			(SIPr)Pd(cinnamyl)Cl	20 min	100
			(IPr)Pd(allyl)Cl	20	31[a]
			(SIPr)Pd(allyl)Cl	20	62[a]
			(IPr)Pd(cinnamyl)Cl	5	100
			(SIPr)Pd(cinnamyl)Cl	5 min	100
			(IPr)Pd(allyl)Cl	20	73[a]
			(SIPr)Pd(allyl)Cl	15	90[a]
			(IPr)Pd(cinnamyl)Cl	6	98
			(SIPr)Pd(cinnamyl)Cl	1.5	97

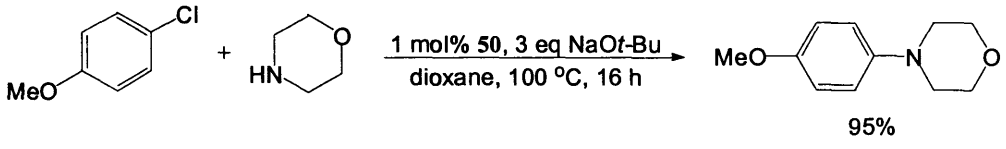
Conditions: 1 mol% complex, 1.1 eq KO*t*-Bu, DME. [a]No further conversion

For example, with (IPr)Pd(cinnamyl)Cl the coupling of 2,6-diisopropylaniline and 2,6-dimethylchlorobenzene was complete within 6 h. However, with (IPr)Pd(allyl)Cl this would not reach completion even after 20 h. But when (SIPr)Pd(cinnamyl)Cl was employed as the catalyst, coupling was complete with 1.5 h. In other cases it was even possible to use as little as 0.01 mol% of the catalyst when working at 80 °C.[41]

Other research groups have also examined the utility of isolated Pd-NHC complexes in amine arylation. For example, in 2005 Gooβen *et al* reported a protocol that made use of commercially available air- and water-stable naphthoquinone imidazolin-2-ylidine-palladium(0) complexes. Initial trials showed the sterically crowded $((IPr)Pd(naphthoquinone))_2$ dimer **50** would mediate amine arylation in near quantitative yields (Scheme 86).[78]



50

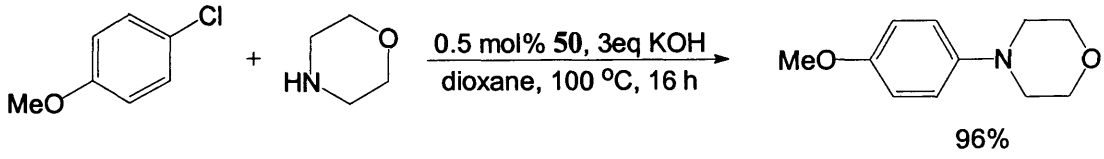


95%

Scheme 86

Further investigations with **50** showed that the sodium *tert*-butoxide base could be replaced: whilst carbonate and phosphate bases were ineffective with this catalyst, near-quantitative yields could be obtained with reagent-grade potassium hydroxide, especially in excess of three equivalents, despite its natural water content of more than

15% (Scheme 87).[79] This was an important improvement in the arylation of alkyl amines, as in most cases, the base is the most expensive reagent to be used.



Scheme 87

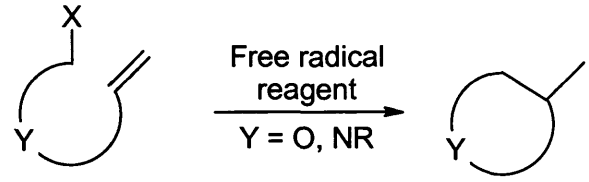
However, hydrolytically unstable substrates failed to react and only modest yields were obtained for halides that possessed an enolisable ketone moiety, although it was found in these cases that sodium *tert*-butoxide afforded better yields. This protocol was found to work well a range of amines with only small levels of bisarylation in reactions encountered when using primary amines.[79]

1.3.7. Summary

The number of subsequent studies on palladium-catalysed amine arylation is a testament to the importance of the early findings of Buchwald and Hartwig. As such, the Buchwald-Hartwig reaction has become an integral part of modern synthetic chemistry. According to a recent review by Ley, the wealth of published material in this area has led to a "toolbox of tuneable reaction conditions whose scope should allow access to most target molecules that incorporate an aryl amine motif."[48] Despite these advances, there is still significant scope for improvements to be made to this reaction, particularly in terms of practicality and reproducibility. Therefore, a new study which has been undertaken to address these issues and others is described in the next section.

2.1 Discussion: Heterocycle Synthesis

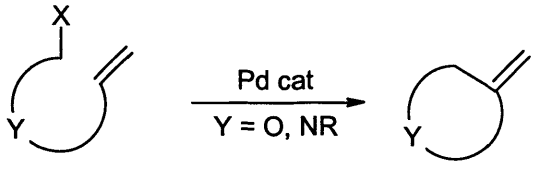
The intramolecular synthesis of heterocycles from alkyl halides with pendant olefin chains is commonly carried out using tin-mediated free radical chemistry (Scheme 88).[79] Yet despite the effectiveness of these techniques, there are a number of disadvantages regarding their use. Not only are tin reagents generally used in stoichiometric amounts, but they are also highly toxic.[80] Whilst less toxic tin-free radical reagents such as EPHP (ethyl piperidine hypophosphate) or TTMSS (tris-trimethylsilylsilane) have also been developed, they are generally less effective than tin reagents, with a large excess of the reagent commonly needed to effectively mediate the desired transformations.[81,82] Furthermore, radical reactions are reductive, with the olefin functionality being lost in the cyclisation. Yet another limitation is that the chloride leaving group is generally not active to radical chemistry, meaning that a bromide or iodide must be used instead.[79] Not only are these groups less atom efficient (due to their higher molecular weight) and are potentially less stable, but they may also be more expensive to prepare than the chloride analogues.



Scheme 88

Because of these limitations, it was postulated that palladium-mediated techniques could be developed as an alternative. Palladium-catalysed reactions are non-reductive and given developments in other areas, it may be possible to develop protocols based on chloride precursors (Scheme 89).[1] Accordingly, a study was embarked upon to

examine the possibility of heterocycle synthesis *via* the intramolecular Heck reaction of alkyl halides. Despite being reported numerous times in the literature with aryl halide substrates,[1,2,9] only a small number of examples of the Heck reaction had been reported utilising saturated halides when this study commenced.[10,13,15-18]



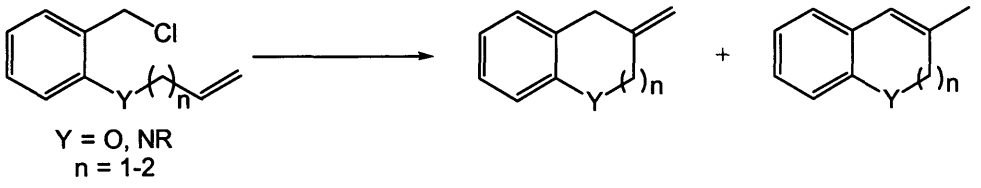
Scheme 89

A suitable starting point for this study was determined to be the manipulations of benzyl halide substrates. Although benzyl halides contain an sp^3 hybridised carbon centre adjacent to the halogen atom, they do not possess β-hydrogens and hence the complications associated with β-H elimination can be avoided. It was hoped in the first instance that the development of reactions of benzyl halides would provide the basis for a more generic methodology utilising any alkyl halide.

2.1.1 Selection of novel benzyl halide Heck substrates

Previous studies by Negishi in 1989 had led to the development of methods for carbocycle synthesis through Heck reactions of benzyl halides with pendant olefin chains.[10] Although this work is clearly related to the present study, it was proposed to use substrates in which the linking chain would incorporate a heteroatom. As it was believed that vinyl substituents would not be of sufficient stability for the proposed manipulations, it was determined that substrates with allyl and homoallyl groups would be prepared in order to form six- and seven-membered rings respectively (Scheme 90).

The decision was also made to employ chloride leaving groups whenever possible. This was the most stable halide leaving group (the least susceptible to hydrolysis) and was reportedly the one most likely to afford selective reactions, where the expected regioisomer in each reaction would be that with an exocyclic olefin moiety.[10]



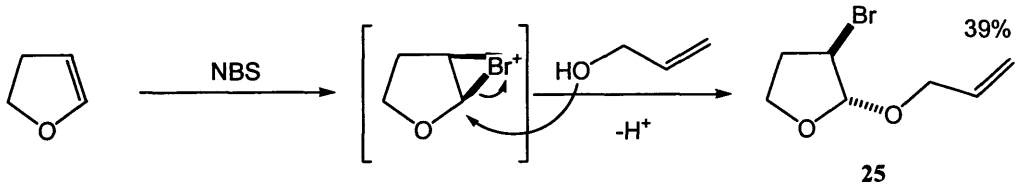
Scheme 90

Although the replacement of a carbon atom with an oxygen or nitrogen atom appeared to be only a superficial alteration, its potentially significant effect on the viability of the process was clear: not only would this enable the potential for palladium-mediated removal of the pendant olefin chains,[83] but it also provided the possibility that the lone pairs on the heteroatoms could suppress reactivity by coordination to other moieties at various points throughout the synthesis (e.g. potential hydrogen bonding to the benzyl alcohol moiety preventing the chlorination step, or coordination to the palladium centre in the Heck reaction effectively acting as a catalyst poison).[84]

2.1.2. Preliminary study.

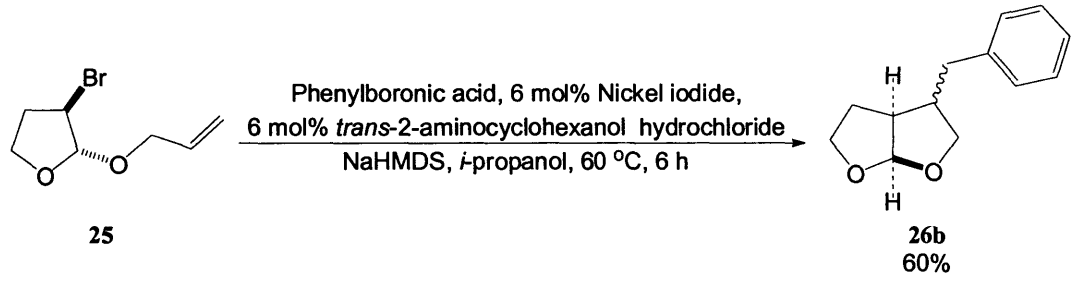
Prior to the commencement of this programme of research, several previously established reactions were examined with the aim of highlighting any further considerations for the proposed novel transformations. This preliminary study was made up of three phases: (i) alternative Ni-catalysed Heck-type reactions, (ii) the Heck reaction of an aryl halide and (iii) the reaction of a benzyl halide in an alternative palladium-catalysed reaction.

Firstly, Fu's reported protocol for a tandem Heck/Suzuki reaction of an alkyl halide with a pendant olefin chain was investigated.[23] This had only been reported as a cascade reaction with a nickel catalyst. Further examination was performed to determine whether it was possible to mediate the process using palladium as opposed to nickel (See section 1.1, Scheme 28).[23] The alkyl halide substrate used by Fu, *trans*-3-bromo-2-allyloxytetrahydrofuran **25**, was prepared by treatment of 2,3-dihydrofuran with NBS and by attack of the resulting intermediate with allyl alcohol (Scheme 91).[85]



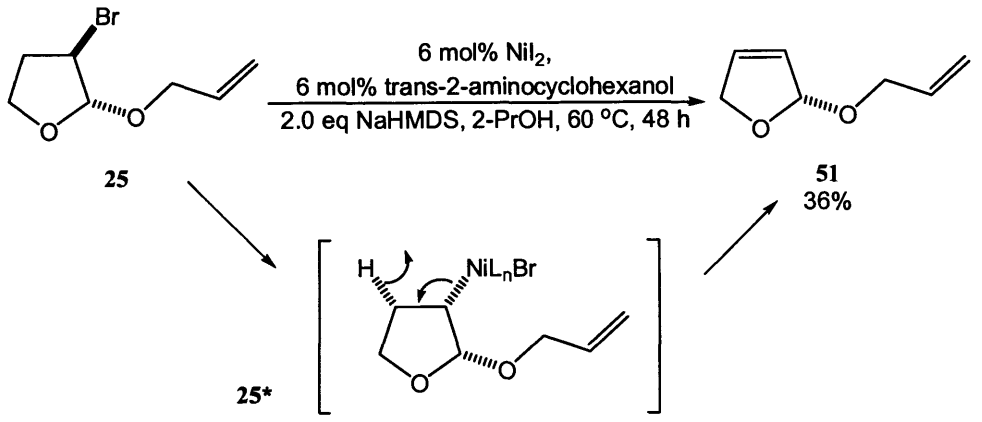
Scheme 91

The tandem Heck-type reaction of **25** was then repeated, affording the desired ring system **26b** in 60% yield (Scheme 92). Despite being lower than the reported yield of 87%, this nonetheless showed the reproducibility of this procedure.[23]



Scheme 92

As it had not been reported,[23] the reaction was then performed without the boronic acid coupling partner, in order to see whether a Heck-type reaction would still occur. In this case cyclisation did not take place: instead the only product observed was that of β–hydride elimination, 2-allyloxy-2,5-dihydrofuran **51** (Scheme 93).



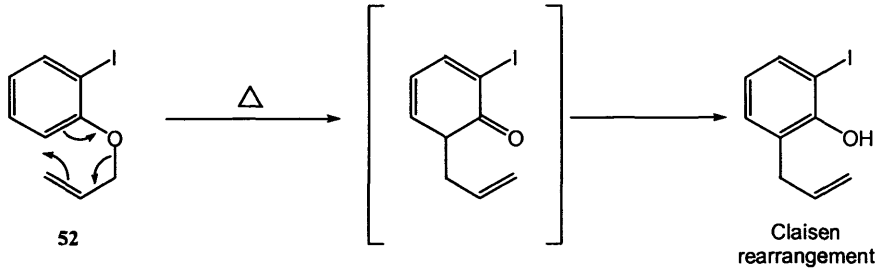
Scheme 93

The most likely mechanism for the formation of **51** would be *via* β-hydride elimination. S_N2 oxidative addition to **25** would have afforded the intermediate **25***, where the nickel moiety was *cis* to the allyloxy group, explaining why β-hydride elimination could not occur with the hydrogen atom in the 2-position of the ring. Such a mechanism casts doubt on Fu's belief that oxidative addition of the active nickel species occurred after the cyclisation.[22,23]

In the absence of the boronic acid, elimination appeared resoundingly to be the favoured reaction. It appeared the boronic acid was acting like the anion capture reagents in Grigg's protocols,[20,21] and that the capture of an intermediate with a boronic acid might also be possible in Pd reactions. However, attempts to repeat either of these reactions using palladium catalysis, were unsuccessful, generally leading to decomposition of **25**. Thus it appeared that a nickel catalyst might be necessary for heterocycle synthesis using an alkyl halide like **25**.[22,23]

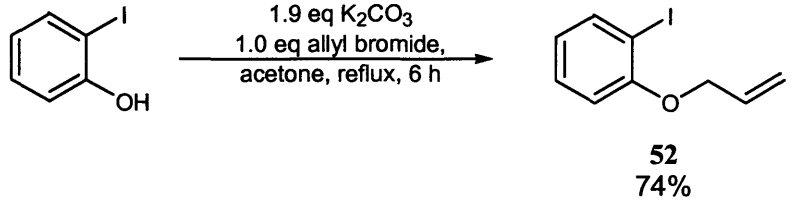
For the second phase of the preliminary study, heterocycle synthesis *via* the intramolecular Heck reaction of an aryl halide was examined, as this would provide information regarding the feasibility of the olefin insertion step in the catalytic cycle.[9]

(2-Iodophenyl)allylether **52** was selected for this purpose, as it had not been utilised in a previous study within the Caddick group.[9] This was another interesting reaction to examine, not only as it would afford the biologically active benzofuran moiety, but also due to the other unwanted transformations that might occur, such as the Claisen rearrangement[86] (Scheme 94) or palladium-mediated deallylation.[83]



Scheme 94

Having conveniently accessed **52** in one step from commercial reagents *via* the allylation of 2-iodophenol (Scheme 95), it was subjected to an *in situ* palladium/imidazolium salt protocol that had previously been developed by Caddick for the Heck reaction.[9]

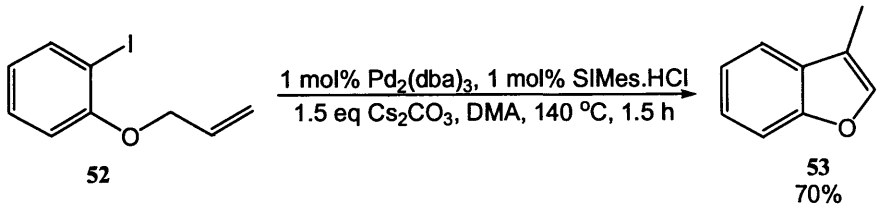


52
74%

Scheme 95

The Heck reaction of **52** to afford 3-methylbenzofuran **53** was complete within 90 min at 140 °C, with only the mildly basic conditions of caesium carbonate necessary for deprotonation (Scheme 96).[9] Despite the high temperature used here, no evidence of a Claisen rearrangement was observed.[86] More importantly, no deallylation was observed either,[83] which suggested that heterocycle synthesis might also be possible

with a benzyl halide moiety instead. This catalytic system was earmarked as a suitable set of conditions to examine for the benzyl halide substrates.[9]



52 **53** 70%

Scheme 96

Having demonstrated the facility of the Heck reaction in an existing protocol,[9] the reactivity of the benzyl halide moiety in palladium-catalysed reactions was investigated next, through the Suzuki coupling of benzyl bromide with 4-methoxyphenylboronic acid. As Suzuki reactions of alkyl bromides with β-hydrogens had been reported,[5] it was hoped that related protocols could also be developed for the Heck reaction of benzyl halide substrates.[10]

Table 9: Suzuki-Miyaura reaction of benzyl halides with 4-methoxyphenylboronic acid.

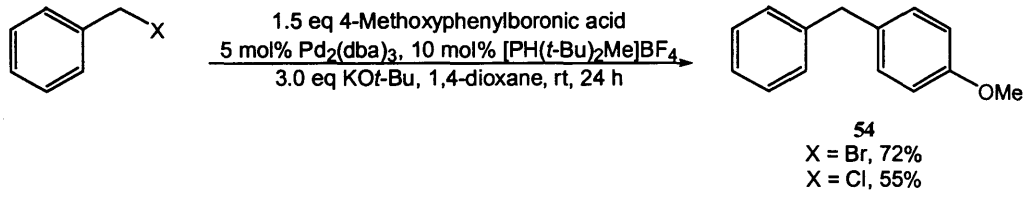
Entry	Halide	Pd source	Ligand	Base	Solvent	Temp/°C	Time/h	Yield
1	BnBr	$Pd_2(dba)_3$	$[PH(t\text{-}Bu)_2Me]BF_4$	KO*t*-Bu	Dioxane	22	24	72%
2	BnBr	$Pd(OAc)_2$	SIPr.HCl	KO*t*-Bu	Dioxane	22	24	-
3	BnBr	$Pd(OAc)_2$	SIPr.HCl	KO*t*-Bu	Dioxane	80	24	-
4	BnBr	$Pd_2(dba)_3$	SIPr.HCl	KO*t*-Bu	Dioxane	80	24	-
5	BnBr	$Pd(PPh_3)_2Cl_2$	-	KO*t*-Bu	Dioxane	22	24	-
6	BnBr	$Pd(PPh_3)_2Cl_2$	-	KO*t*-Bu	Dioxane	80	24	-
7	BnCl	$Pd_2(dba)_3$	$[PH(t\text{-}Bu)_2Me]BF_4$	KO*t*-Bu	Dioxane	22	24	55%

Reaction conditions: 1.0 mmol halide, 1.5 mmol boronic acid, 5 mol% Pd, 10 mol% ligand , 2.0 eq base, 5 mL solvent.

Using the strong base KO*t*-Bu and the alkyl phosphine ligand $P(t\text{-}Bu)_2Me$ in conjunction with the palladium(0) source $Pd_2(dba)_3$, the room temperature coupling of

benzyl bromide with 4-methoxyphenylboronic acid was shown to be possible, affording **6** in 72% yield within 24 h (Scheme 97; Table 9, Entry 1).[5,6] Here, the ligand was employed as a phosphonium salt, which was deprotonated *in situ* to afford the phosphine, avoiding the need for a glovebox.[5,6]

As Caddick and Cloke had reported related protocols for the reactions of alkyl bromides using the imidazolium salt SIPr.HCl, this ligand was also examined.[43] In this case, no reaction was observed, either with Pd(II) or Pd(0) or at an elevated temperature (Table 9, Entries 2-4). The isolated complex $Pd(PPh_3)_2Cl_2$ also appeared to be ineffective (Table 9, Entries 5-6). The alkyl phosphine ligand also enabled the reaction of benzyl chloride, affording **54**, albeit in a reduced yield of only 55% (Scheme 97; Table 9, Entry 7).



Scheme 97

These preliminary reactions showed the potential for novel heterocycle synthesis and also the possible limitations. Newer, more developed, catalysts were shown to lead to success with similar substrates. The conclusion was also reached, that where a palladium-catalysed protocol could not be developed for the new substrates, that radical-mediated procedures should be developed instead.

2.1.3. Development of Heck Reaction Protocol

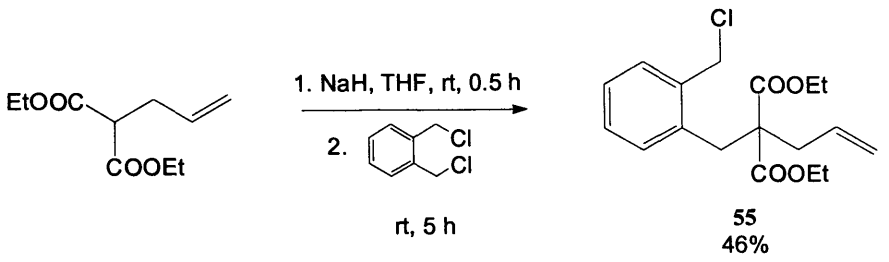
The reported protocol for carbocycle synthesis *via* the intramolecular Heck reaction of benzyl halides was reassessed next, in order to see whether it could be further developed using modern methods.[10] An optimised method would then be applied to the novel substrates. The benzyl chloride **55** was selected for this purpose, as it could be prepared in only one step from commercial reagents and because its reaction afforded only a moderate yield of the desired product.[10]

55 was obtained in 46% yield after 5 h stirring at room temperature after 1,2-dibenzyl chloride was added to a solution of diethyl allylmalonate that had been deprotonated *in situ* using sodium hydride. (Scheme 98).[10]

Table 10: Optimisation of Intramolecular Heck reaction of (2-chloromethylbenzyl)-2-propenylpropanedioic acid diethyl ester **55**.

Entry	Pd catalyst	Ligand	Base	Solvent	Temp/°C	Time/h	Result
1	$Pd(PPh_3)_4$	-	NEt_3	MeCN	22	24	No reaction
2	$Pd(PPh_3)_4$	-	NEt_3	MeCN	90	24	No reaction
3	$PdCl_2(PPh_3)_2$	-	NEt_3	MeCN	90	24	No reaction
4	$PdCl_2(PPh_3)_2$	-	Cy_2Nme	MeCN	90	24	No reaction
5	$PdCl_2(PPh_3)_2$	-	Cs_2CO_3	MeCN	90	24	No reaction
6	$Pd_2(dba)_3$	$[PH(t\text{-}Bu)_2Me]BF_4$	Cy_2Nme	MeCN	90	24	No reaction
7	$Pd_2(dba)_3$	$[PH(t\text{-}Bu)_2Me]BF_4$	Cs_2CO_3	MeCN	90	24	No reaction
8	$PdCl_2(PPh_3)_2$	-	NEt_3	MeCN	90 μwave	20 min	63% exo, 23% halide
9	$PdCl_2(PPh_3)_2$	-	Cy_2Nme	MeCN	90 μwave	20 min	95% (*exo* only)
10	$Pd_2(dba)_3$	$[PH(t\text{-}Bu)_2Me]BF_4$	Cy_2Nme	MeCN	90 μwave	20 min	No reaction
11	(SIPr)Pd(methallyl)Cl	-	Cy_2Nme	MeCN	90 μwave	20 min	No reaction

Reaction conditions: 0.2 mmol halide, 5 mol% Pd, 10 mol% ligand (where applicable), 2.0 eq base, 1.5 mL solvent



Scheme 98

However, using the reported conditions (5 mol% $Pd(PPh_3)_4$, 2.0 eq Et_3N base in acetonitrile solvent),[10] the Heck reaction did not occur (Table 10, Entries 1-2), highlighting a the capriciousness of palladium chemistry. Further conditions would have to be screened.

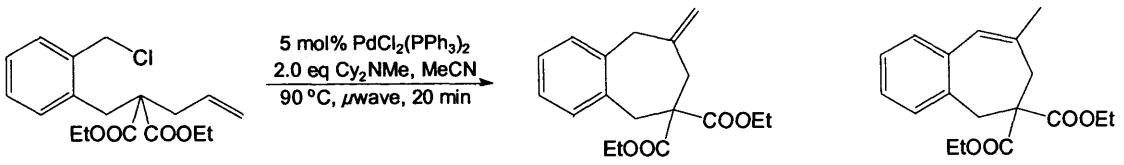
It was of particular concern that the stability and thus reliability of tetrakistriphenylphosphine palladium(0) could be affecting the reaction.[87] Accordingly, the reaction was repeated using the alternative palladium complex used by Negishi, *trans*-dichlorobis(triphenylphosphine)palladium(II).[10] Although this complex is often found to be less active than tetrakistriphenylphosphine palladium(0), being a palladium(II) complex, it has the advantage of being shelf-stable and hence more reliable:[87] thus it was thought that this would be a more accurate measure of the reproducibility of the Heck reaction. However, even with $PdCl_2(PPh_3)_2$, the reaction still failed to occur at 90 °C (Table 10, Entry 3).

As the correct choice of base is often key to the success of palladium reactions, further bases were screened. It was hoped that *N*,*N*-dicyclohexylamine would enable cyclisation, as it had been reported to be the preferred base in the Heck reaction of aryl halides.[4] As it is more hindered than triethylamine, there is less opportunity for the base to coordinate to the Pd metal centre, which may hinder the catalytic

process.[84] However, even with this base, the Heck reaction still failed to occur (Table 10, Entry 4). This was also the case with the inorganic base cesium carbonate, which had also been recommended for the reaction (Table 10, Entry 5).[9,13]

Following the success with the alkyl phosphonium salt $[PH(t\text{-}Bu)_2Me]BF_4$ as ligand precursor in the Suzuki reaction of benzyl chloride, it was anticipated that it might also mediate the Heck reaction of **55**. However, even with this system, using either Cy_2NMe or Cs_2CO_3 as base, the reaction still failed to occur at 90 °C (Table 10, Entries 6-7).

As it was apparent that conventional methods would not afford the desired transformation, it was hoped that microwave enhancement might be the key to successfully mediating the reaction.[88] Therefore, the reaction was repeated with the reported reagents at 90 °C in a commercial laboratory microwave reactor. Following heating for 20 min, the reaction was found to be successful, affording the desired exocyclic product **56** in 63% yield, with the endocyclic product **57** not being observed. However, 23% of the unreacted halide was also recovered, showing that these conditions were not sufficient for the reaction to proceed to completion (Table 10, Entry 8). Accordingly, the more hindered base Cy_2NMe was utilised in place of triethylamine. Following heating for 20 min at 90 °C, the exocyclic product **56** was selectively obtained in 95% yield, with the halide fully consumed (Scheme 99; Table 10, Entry 9).



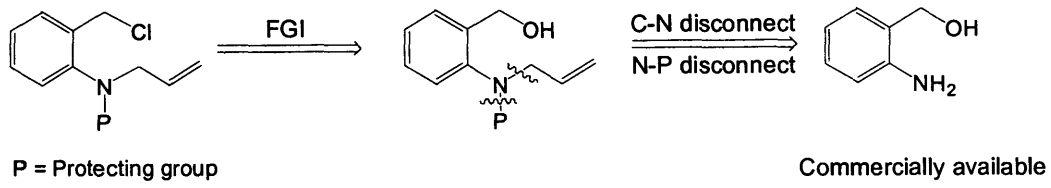
55 **56** 95% **57** Not observed

Scheme 99

Considering that no conversion took place using conventional heating techniques (i.e. with the use of an oil bath), the conclusion was drawn that the microwave reactor was enhancing the reaction.[88] An explanation for this enhancement may be that it was a result of efficient, concentrated heating in a sealed vessel at a higher than atmospheric pressure, rather than it being as result of a specific microwave effect.[88] It was then anticipated that these conditions could be used in the reactions of the novel benzyl halides in the synthesis of heterocycles.

2.1.4. Benzyl halide preparation

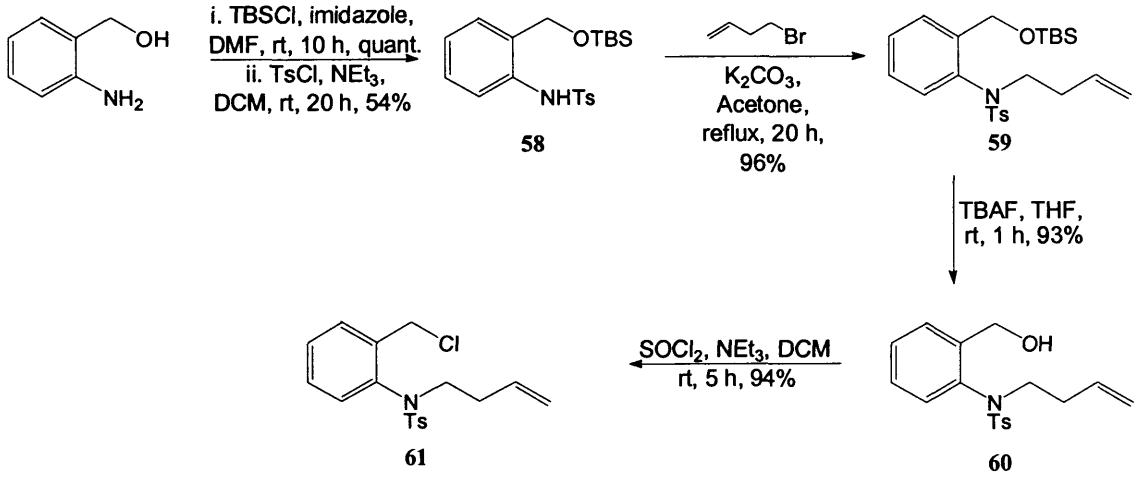
For the development of the new substrates, those that would afford seven-membered rings were prepared first (c.f. the reaction of **55**). In the preparation of the *N*-analogue, protection was deemed to be necessary on the nitrogen to prevent any intermolecular reaction of the N-H moiety with the benzyl chloride. Simple retrosynthetic analysis showed that potential substratres could be accessed from the commercially available 2-aminobenzyl alcohol (Scheme 100). It was also clear that alcohol protection would be needed to prevent the competing side reaction of *O*-alkylation. The decision was taken to use TBS (*tert*-butyldimethylsilyl) protection due to its convenience, both in terms of introduction and removal.[89]



Scheme 100

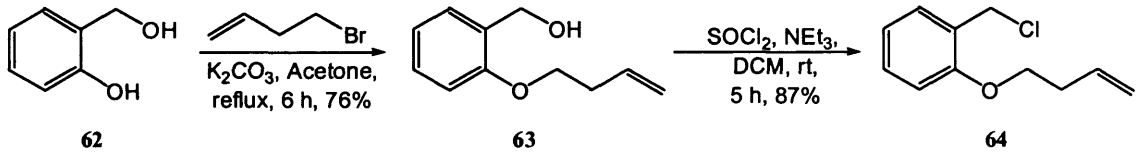
Due to its electronic properties and because of an existing literature protocol for part of its synthesis,[90] tosylate (*p*-Tol-SO_2-) was selected for *N*-protection. It was hoped that the highly electron-withdrawing ability of this group would prevent the nitrogen lone pair from affecting reactivity.[84]

In the first step of the synthesis, TBS alcohol protection of 2-aminobenzyl alcohol was performed in a quantitative yield (Scheme 101).[89] Tosylation was performed using tosyl chloride in conjunction with triethylamine base to give **58** in a modest yield of 54%. Whilst it was reported that pyridine was a more effective base in this reaction,[91] triethylamine was preferred due to the hazards and strong odour associated with the former. Homoallylation to prepare **59** was performed with homoallyl bromide and potassium carbonate in near quantitative yield within 20 h under reflux in acetone.[92] Deprotection of the silyl ether with TBAF[89] to afford **60** was problem-free and was followed by a high-yielding chlorination step with thionyl chloride to afford the Heck reaction substrate **61**.[93]



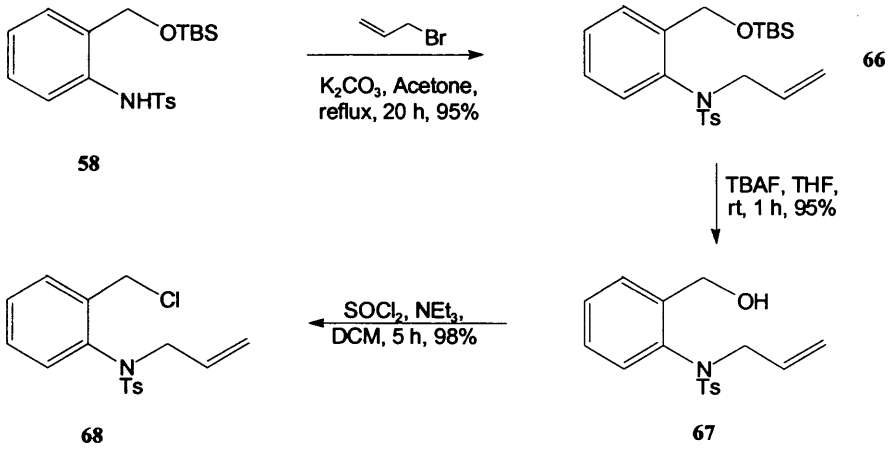
Scheme 101

Due to the disparity in pKa between the phenol and benzyl alcohol moieties,[94] selective alkylation of the phenol moiety was possible in the preparation of the *O*-homoallyl analogue, without the need for any protecting groups. As such, the substrate was prepared in only two steps: homoallylation of saligenin **62** in 76% yield, followed by chlorination of the alcohol moiety on **63** to afford **64** in 87% yield (Scheme 102).[92,93]



Scheme 102

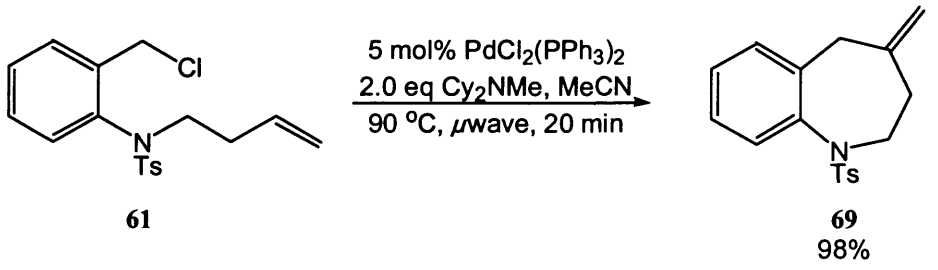
With two homoallyl substituted substrates successfully prepared, the allyl-substituted benzyl chloride **65** was prepared next, as this would potentially afford a six-membered ring (Scheme 103). This was performed *via* a similar process, as **58** underwent allylation in 95% yield affording **66**.[92] The alcohol **67** was formed through deprotection of the silyl group with TBAF in 95% yield, which was followed by chlorination to form the halide **68** in a yield of 98%.[92,93]



Scheme 103

2.1.5. Attempted Heck Reactions.

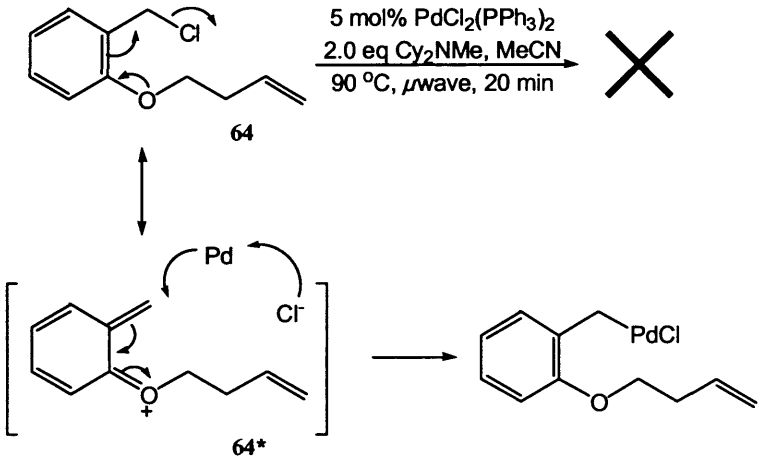
Initially, the Heck reaction of **61** was attempted using the microwave-enhanced protocol developed for Negishi's substrate **7**.[10] **61** underwent the Heck reaction using the newly-developed conditions, selectively forming the substituted benzazepine **69**, where the olefin bond remained exocyclic, in 98% yield (Scheme 104).



Scheme 104

This was a key result in this study, showing that heterocycle synthesis was possible using the intramolecular Heck reaction of benzyl halides. Attempts to successfully perform this transformation under different conditions however did not bear fruit: reactions using imidazolium or phosphonium salts, or the (SIPr)Pd(methallyl) complex, failed to react at all, with **61** simply being recovered.

Having demonstrated the reaction of **61**, the cyclisation of the *O*-variant **64** was examined next. However, the same conditions that had mediated the reactions of **55** and **61** were ineffective here, as the starting material **64** was recovered following reaction in the microwave at 90 °C (Scheme 105). This was an unexpected finding, as unlike **55** and **61**, the aryl ether **64** had the potential to form the resonance structure **64*** which would be expected to result in a more facile oxidative addition step. The use of solvents of differing polarity, including THF, 1,4-dioxane and DMF also failed to mediate the reaction.

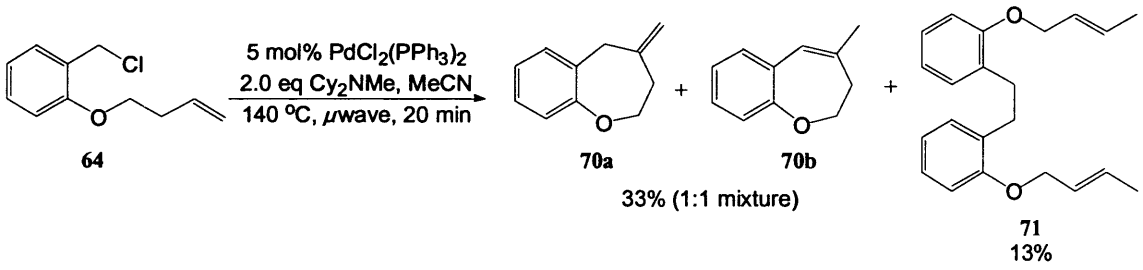


Scheme 105

The greater activity of **55** and **61** in comparison to **64** was believed to be due to the Thorpe-Ingold effect, whereby the steric bulk of the ester and tosyl groups resulted in an increase in strain and a reduction in the entropy of rotation for the linking chains. This meant that they were more likely to assume a suitable conformation in which to undergo carbometallation.[95]

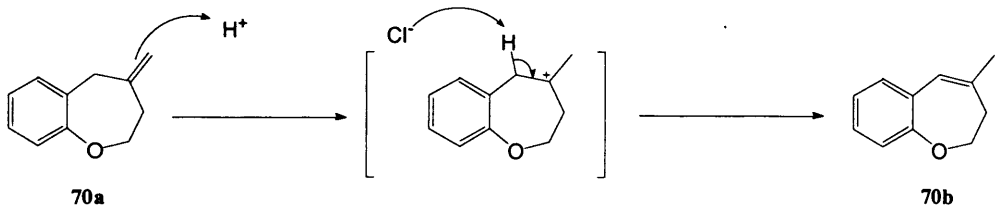
However it was found that the cyclisation of **64** would proceed in a similar timeframe to **61** when irradiating at 140 °C. Whilst the additional energy supplied by heating at 140 °C appeared to overcome the lack of a favourable Thorpe-Ingold effect,[95] it also

promoted unwanted reaction pathways, as **70a** and **70b**, the exocyclic and endocyclic Heck products respectively, were afforded as a 1:1 inseparable mixture in 33% yield (Scheme 106).



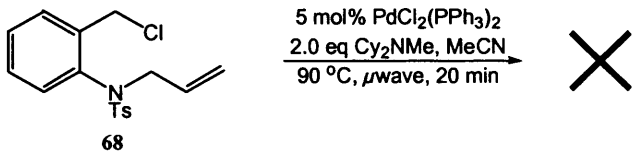
Scheme 106

As postulated by Negishi, it is likely that the rearrangement of **70a** into **70b** was mediated by the HCl formed in the formation of **70a** (Scheme 107).[10] **71** was also obtained in 13% yield. It appeared that this was formed as an apparent result of Pd-mediated homocoupling[96] and rearrangement of the homoallyl chain.



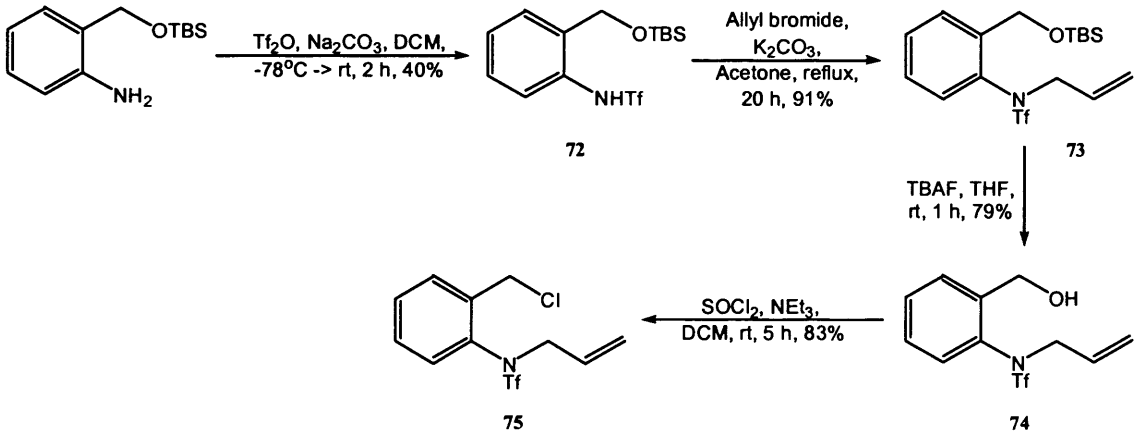
Scheme 107

With the preparation of two seven-membered rings exemplified, the focus of the study shifted to the reaction of **68**, which would potentially afford a six-membered ring. However, no reaction occurred using the preferred reagents either at 90 °C or 140 °C (Scheme 108). Interestingly, in both cases, **68** was almost entirely recovered, showing that Pd-mediated deallylation was not preventing the desired reaction.[83]



Scheme 108

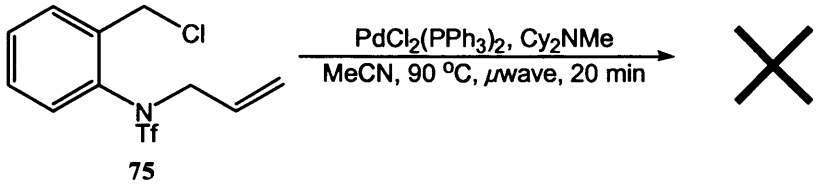
In order to determine whether the tosyl protection was in any way responsible for the reaction not taking place, an analogue of **68** with the more electron-withdrawing triflate (F_3CSO_2-) protection was also examined. This was prepared in five steps starting from 2-aminobenzyl alcohol (Scheme 109). Following TBS protection,[89] reaction with triflic anhydride under basic conditions afforded the triflic amide **72** in 40% yield.[97] This was followed by the high-yielding steps of allylation (**73**), TBS deprotection (**74**) and alcohol chlorination to obtain **75**.[89,92,93]



Scheme 109

However, as with **68**, the attempted Heck reaction of the *N*-triflate analogue **75** was unsuccessful, both at 90 °C and 140 °C (Scheme 110), where near quantitative recovery of the substrate was again possible. Accordingly, further conditions were examined, with imidazolium and phosphonium salt protocols failing to mediate the Heck reaction, either with Pd(0) or Pd(II). This was also the case with the isolated complexes (SIPr)Pd(methallyl)Cl and POPd, where recovery of **75** was still possible.

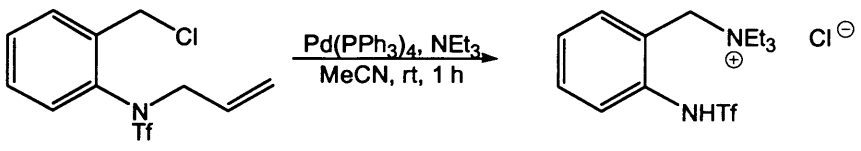
The replacement of acetonitrile with the less polar THF and the use of the inorganic base cesium carbonate[9] did not improve the viability of the reaction.



75

Scheme 110

Interestingly, when using the conditions reported by Negishi, of $Pd(PPh_3)_4$ with triethylamine as base, reaction occurred at room temperature.[10] However, rather than the desired Heck product, repeated trials led to the isolation of **76** (Scheme 111). This was formed as a result of two unwanted side reactions, namely palladium-catalysed deallylation[83] and substitution of the chloride moiety with triethylamine to afford a quaternary ammonium salt.[98] This transformation was not observed with any palladium catalyst other than $Pd(PPh_3)_4$, clearly suggesting that this complex was not suitable for use in this study, possibly as the excess triphenylphosphine present in the mixture was acting as a nucleophile..



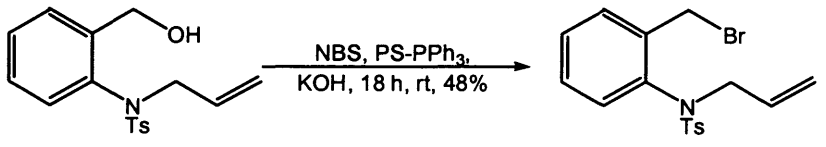
75 76
26%

Scheme 111

2.1.6. Alternative methods for cyclisation of benzyl halides

As the Heck reaction did not lead to the desired six-membered heterocycles, it was postulated that other related techniques, specifically those utilising radical mechanisms, might offer success instead.[23-27,79,80] As these protocols do not generally permit the use of chlorides, attempts were made to prepare benzyl bromide analogues of **68** and **75** instead.

Efforts at isolating a triflate-substituted benzyl bromide analogue were not successful. LC-MS analysis suggested that the formation of the bromide was possible, but it appeared to be somewhat unstable, as attempts at chromatography only yielded its alcohol precursor. As such, the investigation into radical-mediated reactions utilised the tosyl analogue **77**. NBS, polymer-supported triphenylphosphine and ground potassium hydroxide were utilised to successfully prepare this substrate (Scheme 112).[99] They were easily removed in work-up and silica gel chromatography to allow the isolation of **77**. Whilst this was only possible in a modest yield of 48%, this was nonetheless preferable to attempts with the triflate analogue where isolation was deemed to be non-trivial.

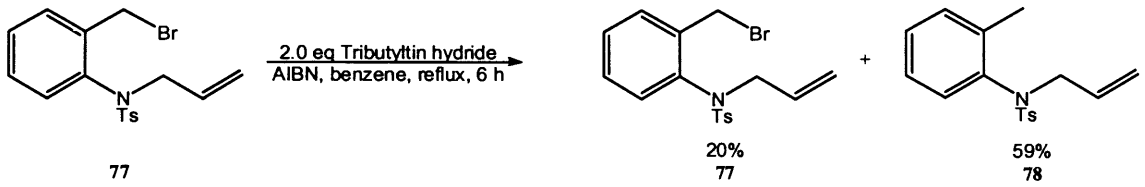


77

Scheme 112

It was hoped that cyclisation might be possible using the established technique of tin-mediated free-radical chemistry.[79-80] **77** was heated under reflux with two equivalents

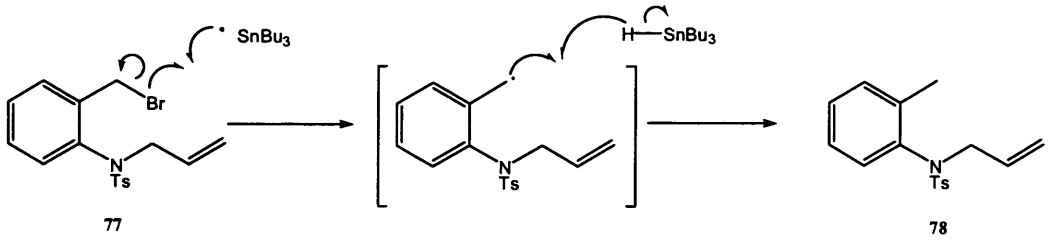
of tributyltin hydride and AIBN in benzene for 6 h, with the tin reagent being added to the reaction mixture in its entirety at the start of the reaction (Scheme 113).



77 20% 77 59% 78

Scheme 113

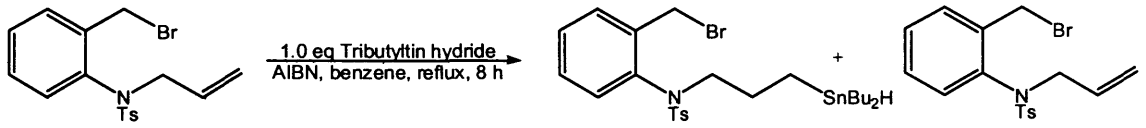
Two major products were isolated from this reaction, namely 20% yield of recovered **77** and 59% of 2-(*N,N*-allyltosylamino)toluene **78**, which formed as a result of hydrodehalogenation. The formation of **78** was preferred to cyclisation, as the addition of TBTH in one portion resulted in a high concentration of the radical species (Scheme 114).[79,80]



77 78

Scheme 114

As it was hoped that a lower concentration of the tin species would promote cyclisation, the reaction was repeated with only one equivalent of tributyltin hydride. However, the stannane **79** was obtained in 33% yield as a result of the tin reagent adding across the olefin bond (Scheme 115). This was similar to the results of the TBTH reactions reported by Negishi on benzyl halides.[10]

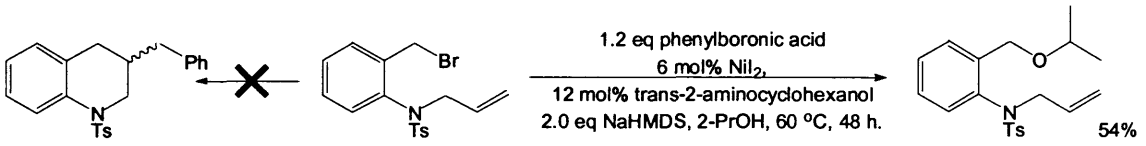


77 33% 79 42% 77

Scheme 115

Dropwise addition of one equivalent of the tin reagent, which resulted in even lower concentrations in the reaction mixture, also failed to promote the intramolecular reaction, again affording **79** in 36% yield.

Having shown that tin radical conditions were not suitable for this benzyl halide, it was next subjected to the conditions for the reported tandem cyclisation/Suzuki reaction.[23] This was expected to furnish the substituted quinoline **80** (Scheme 116).



80 77 81

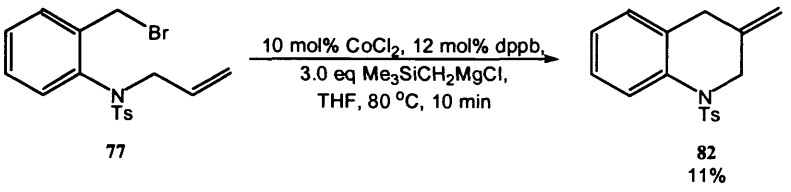
Scheme 116

However, no cyclisation was observed in this reaction. Instead the only product isolated was the *iso*-propylbenzyl ether **81** (Scheme 116). This was formed by nucleophilic substitution of the base sodium *iso*-propoxide (formed from NaHMDS and the *iso*-propanol solvent) at the benzyl carbon centre, replacing the bromide leaving group. Even with the boronic acid coupling partner, cyclisation was not favoured with this protocol for **77**.[23]

Failure to obtain the desired product in the nickel-catalysed reaction resulted in the examination of further radical techniques. Accordingly, methodology reported by Oshima, consisting of treatment with a Grignard reagent (Me_3SiCH_2MgCl) in the

presence of a cobalt catalyst, was utilised.[24-26] As Oshima had reported intramolecular Heck-type reactions of alkyl iodides and intermolecular Heck-type reactions of benzyl bromides, it was hoped that this methodology might be successfully applied to **77**.[24-26]

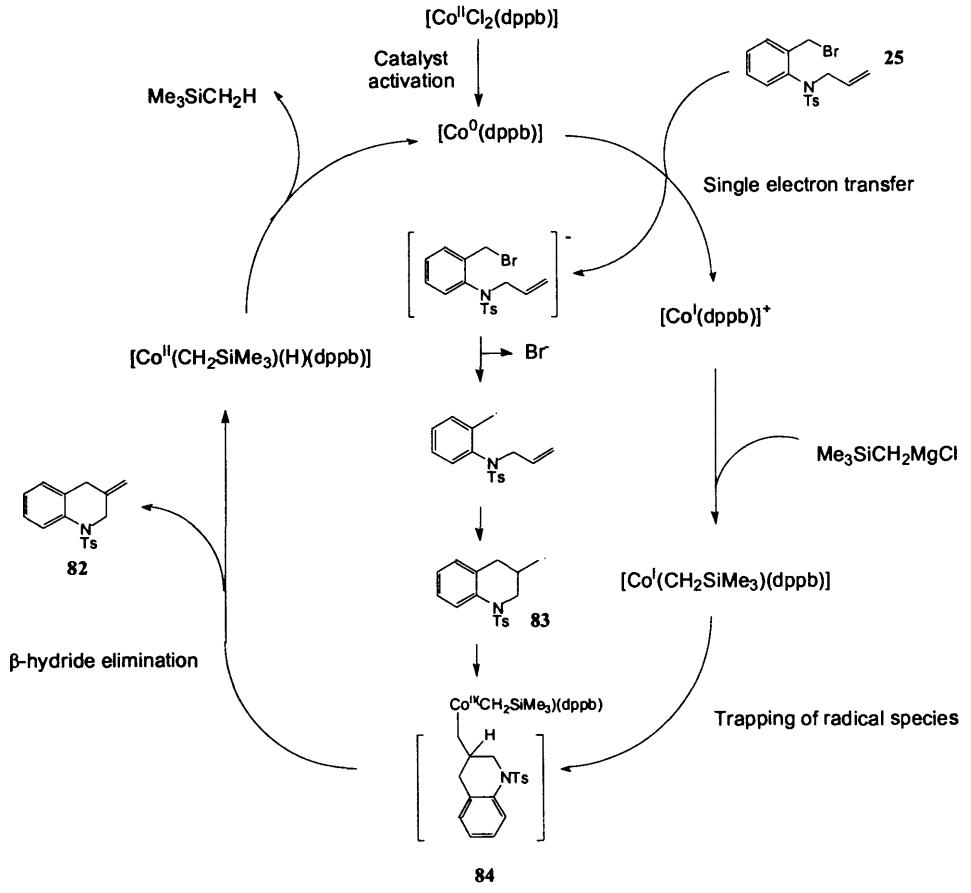
77 was heated under reflux in THF with $CoCl_2$(dppb) and Me_3SiCH_2MgCl for 10 min, in which time it was fully consumed. The desired Heck-type product **82**, where the double bond was exocyclic, was obtained in 11% yield (Scheme 117). Although this was a somewhat low yield, it was nonetheless a pleasing result, as it showed that substituted tetrahydroquinolines would be accessible from benzyl halide precursors.



77 **82**
11%

Scheme 117

It was assumed that **82** was formed *via* a mechanism reported by Oshima (Scheme 118), whereby the proposed active species [Co^0(dppb)] would have effected single electron transfer to **77**, forming an anion radical of the halide.[24-26] This would be followed by immediate loss of the bromide anion and cyclisation of the resulting radical species to form **83**.[24-26]



Scheme 118

The Rradical **83** would undergo trapping with the cobalt complex $[Co^{I}(CH_2SiMe_3)(dppb)]$ to form the intermediate **84**.[24-26] Finally, Oshima's proposed mechanism would have resulted in β-hydride elimination to afford the Heck-type product **82** and loss of tetramethylsilane to regenerate the active species $[Co^{0}(dppb)]$.[24-26]

2.1.7. Conclusions

In this study, a reproducible practical procedure that utilised microwave irradiation was developed in order to perform the intramolecular Heck reaction of benzyl halides. This new procedure improved upon the reported synthesis of a carbocycle[10] and enabled efficient access to potentially useful heterocyclic products.

Additionally, reinvestigation of Fu's nickel-catalysed work showed its reliance on the boronic acid coupling partner to effect the desired (and presumably radical) reaction and that it was not amenable to the benzyl halide substrates.

Overall, while it was found that palladium chemistry may have limitations in this field, it has been shown to have significantly more potential than the highly toxic, yet established, methods of tin radical chemistry. It is now hoped that future work will entail the palladium-catalysed reactions of benzyl halides to form rings of other sizes and that further endeavours will enable heterocycle synthesis *via* the cyclisation of alkyl halides with β-hydrogens.[1]

2.2: Discussion: Amine Arylation

2.2.1 Aim of study

As outlined in the introduction (*vide supra*), substantial research has been undertaken into *N*-heterocyclic carbene (NHC) ligands as potential phosphine replacements. Whilst a plethora of Pd-NHC protocols have been developed, the majority have been reported from an inorganic or organometallic chemistry perspective, with procedures commonly conducted using an inert atmosphere glovebox. Although this has allowed the development of superb coupling protocols, the requirement of a glovebox or very specific and rigorous purification of reagents has limited the broader appeal of these techniques.

A common concern in amine arylation has been the employment of alkoxide bases. These bases are often used due to their moderate economic cost and the fact that they are the mildest possible bases that can regularly be used in this reaction. Unfortunately, alkoxide bases must be sublimed twice and stored in a glovebox in order to ensure their activity.[73] Alternatively, an excess must be employed, which of course negates any economic advantages. In fact, it was discovered in an earlier study that the reproducibility of Buchwald-Hartwig reactions is critically dependent upon the quality of the alkoxide that is used. Even when stored in a glovebox, the widely-used potassium *tert*-butoxide (KO*t*-Bu) was less effective after a period of a few months than after it had been freshly sublimed.[73,100]

As a result of difficulties like this, Pd-NHC techniques taken from the literature have the stigma of being potentially unreliable and irreproducible, as when

chemicals are weighed out in air and reactions are performed under less stringent conditions, there may be a drop in the yield of a reaction. This often leads to the use of the inefficient, yet "tried and tested", but in fact often sub-optimal, palladium-phosphine complexes like $Pd(PPh_3)_4$ instead. It is likely to be more than just coincidence that industrial endeavours in this field have generally exploited phosphines in bench-scale research and large-scale manufacture.[66]

Nevertheless, whilst most amine arylation has been conducted at temperatures in excess of 80 °C,[57,66] or under microwave irradiation,[73] room temperature Pd-NHC procedures are now becoming much more commonplace. In fact, much of the emphasis of research has been put upon the range of halides that may be coupled, rather than amines. Instead, the coupling needs to be considered as the *functionalisation of amines* in order to fully develop reliable protocols that may be used regularly in industry, where more elaborate and less reactive amines are encountered on a regular basis, particularly in the development of novel compounds for biological testing.

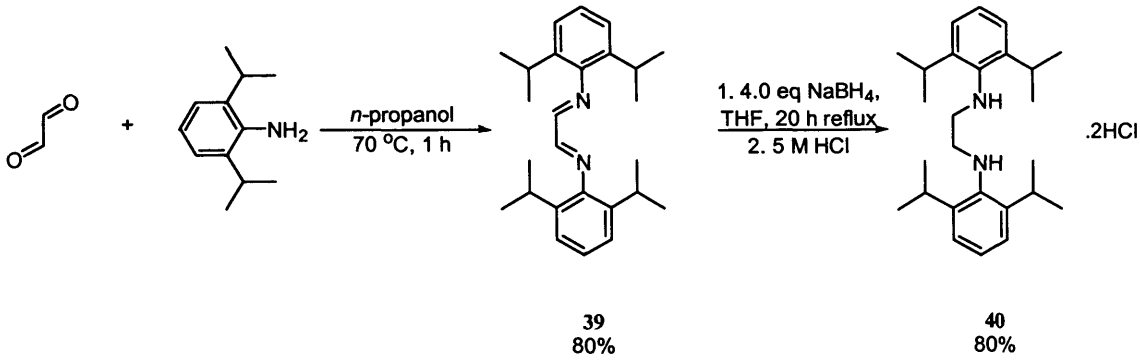
For this reason, the decision was made to further investigate the Buchwald-Hartwig reaction. A study was undertaken to oversee the development of a practical and efficient (ideally room temperature) reaction protocol based on the arylation of amines, with the eventual aim of a general procedure whereby any aryl halide might be coupled with any molecule containing the N-H moiety using Pd-NHC catalysis.

It was hoped initially that this would be possible with the practical use of a palladium source and an imidazolium salt, where the active catalytic species would be formed *in situ* (see section 1.3.4.).

2.2.2. Preparation of saturated imidazolium salts

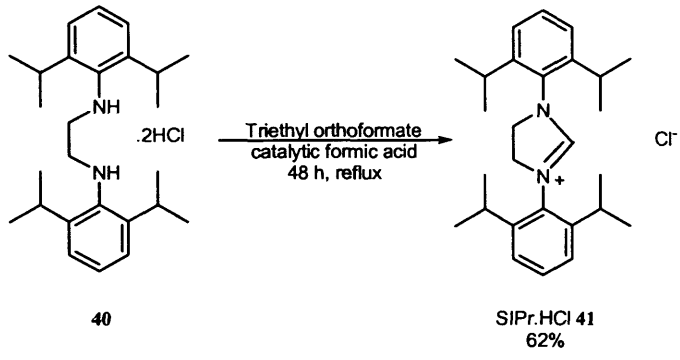
Whilst a variety of imidazolium salts and Pd-NHC complexes are commercially available, their preparation is an inexpensive means of preparing the larger quantities needed for optimisation studies. As previous research within the Caddick and other research groups had shown *N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) to be the preferred ligand in the Buchwald-Hartwig reaction,[57,59,73] the decision was taken to use this ligand throughout this programme of research. Accordingly, the corresponding saturated imidazolium salt 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr.HCl) was prepared for the first phase of the study, using the convenient procedure reported by Arduengo (see section 1.2.3.).[36]

For the first step in the preparation of SIPr.HCl, the condensation of 2,6-diisopropylaniline with aqueous glyoxal was carried out to afford glyoxal-bis(2,6-diisopropylphenyl)imine **39** in 80% yield (Scheme 119). **39** was then reduced to the corresponding diamine with sodium borohydride. As per the published procedure,[36] the diamine was isolated as the dihydrochloride salt **40** in 80% yield, following the addition of an excess of concentrated hydrochloric acid. As **40** was a crystalline solid, no column chromatography was necessary, as it was possible to obtain a pure sample *via* recrystallisation (Scheme 119).



Scheme 119

SIPr.HCl **41** was then obtained by heating **40** in an excess of triethyl orthoformate with catalytic formic acid in 62% yield. Here, the triethyl orthoformate acted both as the reaction solvent and as a carbon building block (Scheme 120).[36]



Scheme 120

2.2.3 Optimisation Study Of *in situ* Imidazolium Salt Protocol

Having prepared a reserve of SIPr.HCl, it was possible to examine its role as an ancillary ligand in amine arylation. As a starting point towards developing a general protocol, it was decided first to specifically investigate aryl bromide substrates, due to a shortage of general procedures for this supposedly more facile type of substrate.

Optimisation was carried out using two simple coupling substrates, bromobenzene and piperidine (Table 11). The dimeric palladium(0) source $Pd_2(dba)_3$ was selected

here, as previous research had shown it to effectively mediate the coupling of aryl bromides.[9] A loading of 1 mol% $Pd_2(dba)_3$ was employed, along with 4 mol% SIPr.HCl. The 1:2 ratio of palladium to ligand was equivalent to that which would be found in the biscarbene complex $Pd(SIPr)_2$, which was believed to form *en route* to the active species (SIPr)Pd(0).[55-57]

Table 11: Buchwald-Hartwig coupling of PhBr and piperidine (1 mol% $Pd_2(dba)_3$, 4 mol% SIPr.HCl **41**): Effect of Pd(0), Base, Solvent and Temp.

Entry	Base	Solvent	Temp/°C	Time/h	Yield/%
1	1.5 eq Cs_2CO_3	1,4-dioxane	80	24	-
2	1.5 eq Cs_2CO_3	DMA	140	24	-
3	2.0 eq KO*t*-Bu	DME	100	2.5	94
4	1.5 eq KO*t*-Bu	DME	22	48	17
5	2.0 eq KO*t*-Bu	DME	22	48	53
6	2.0 eq KO*t*-Bu	1,4-dioxane	22	28	78
7[a]	2.0 eq KO*t*-Bu	1,4-dioxane	22	24	-
8	2.0 eq KO*t*-Bu	1,4-dioxane	μwave	10min	98
9[b]	2.0 eq KO*t*-Bu	1,4-dioxane	μwave	10min	93
10	**1.5 eq LHMDS**	**THF**	**22**	**20**	**89**
11	1.5 eq LHMDS	THF	80	1.5	93
12	1.5 eq LHMDS	THF	μwave	10min	Quant.

Conditions: PhBr (1.0 mmol), piperidine (1.2 mmol), 1 mol% $Pd_2(dba)_3$, 4 mol% SIPr.HCl, base, 1.0 mL-1.5 mL solvent. [a] $Pd(dba)_2$. [b] 0.5 mol% Pd.

Initially, reactions were carried out with caesium carbonate base at 80 °C and 140 °C (Table 11, Entries 1-2). Both trials were unsuccessful which supported the assertion that the complex formed after amine association is only mildly Lewis acidic: it was clear that a stronger base would be needed.[56] Next, potassium *tert*-butoxide was screened as base, with two equivalents employed to compensate for it being used as

purchased. In this case, the desired aniline was obtained in a high yield in only 2.5 h at 100 °C (Table 11, Entry 3).

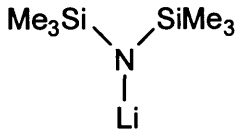
Disappointingly, when the reaction was repeated at room temperature, the yield dropped significantly (Table 11, Entries 4-5). However, switching the solvent from DME to 1,4-dioxane considerably enhanced the yield of the room temperature reaction (Table 11, Entry 6).

Next, the monomeric $Pd(dba)_2$ was tested as an alternative to $Pd_2(dba)_3$, as it had been the recommended source of palladium in other published protocols.[56] However, this Pd(0) source resulted in no reaction taking place (Table 11, Entry 7). An explanation for this might be that $Pd(dba)_2$ contains a lower palladium/ligand ratio than the dimer, which could potentially limit the rate of dba dissociation.

Interestingly, it was demonstrated that microwave heating would greatly accelerate the reaction, even allowing the opportunity for lower catalyst loading (Table 11, Entries 8-9).[88] As in the Heck study, this was assumed to be due to efficient heating of the solvent in a sealed vessel above atmospheric pressure.

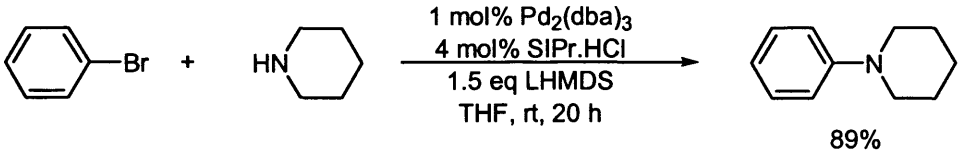
Nevertheless, as the primary aim of this study was to develop a room temperature protocol, further conditions were examined that might enhance room temperature coupling. As it had already been observed that the choice of base was key to the reaction, lithium hexamethyldisilazide (LHMDS; Scheme 121) was examined. This was conveniently available as a 1 M solution in THF. Although successful with Pd-

phosphine systems,[54,55] this stronger base (pka ~ 30-35) had never been examined under Pd-NHC catalysis.



Scheme 121 - LHMDS

In a key reaction, the use of LHMDS as base led to a room temperature conversion that was faster and higher yielding than that with the butoxide base, as 89% yield of the aniline product was isolated after a reaction time of 20 h (Table 1, Entry 10; Scheme 122). Thermal heating and microwave heating also resulted in faster reactions with higher yields with the use of LHMDS (Table 1, Entries 11-12). With a suitable set of conditions developed, it was possible to examine the scope of the reaction.

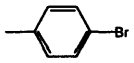
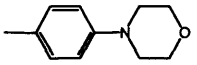
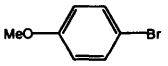
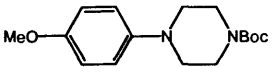
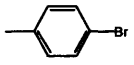
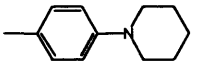
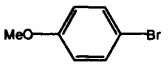
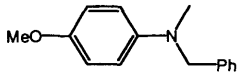
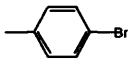
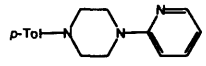
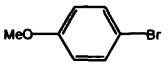
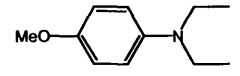
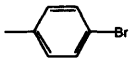
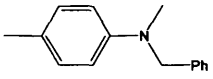
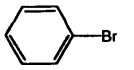
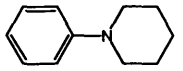
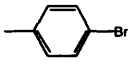
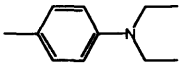
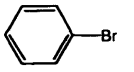
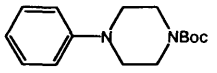
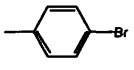
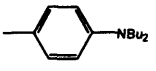
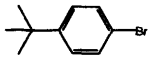
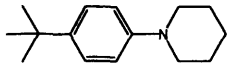
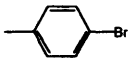
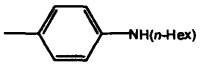
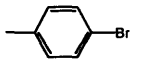
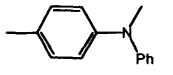
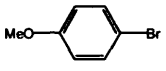
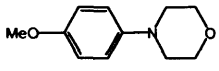
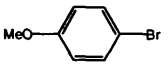
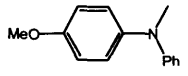
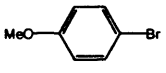
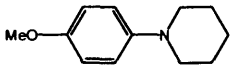
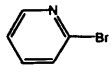
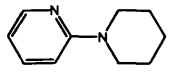


Scheme 122

2.3.4. Examining the Scope of the Imidazolium Salt Protocol.

As expected, the best results with this protocol were obtained in reactions with cyclic secondary amines. These amines are highly reactive in amine arylation due to their abilities as good nucleophiles, with their cyclic structures locking them into conformations suitable for association to the metal centre.[101] The fastest reactions observed were those of 4-bromotoluene with morpholine (7 h) and piperidine (10 h) in yields of 89% and 98% respectively (Table 12, Entries 1-2).

Table 12: Buchwald-Hartwig reactions of aryl bromides using the Pd/imidazolium salt protocol[a]

Entry	Halide	Product	Time/ h	Yield/ %	Entry	Halide	Product	Time/ h	Yield/ %
1			7	89	10			20	86
2			10	98	11			48	75
3			24	66	12			72	54
4			24	73	13			20	89
5			20	74	14			20	88
6			120	17[b]	15			96	18
7			24	61[c,d]	16			48	98[c]
8			24	78	17			72	83[c]
9			24	88	18			48	73

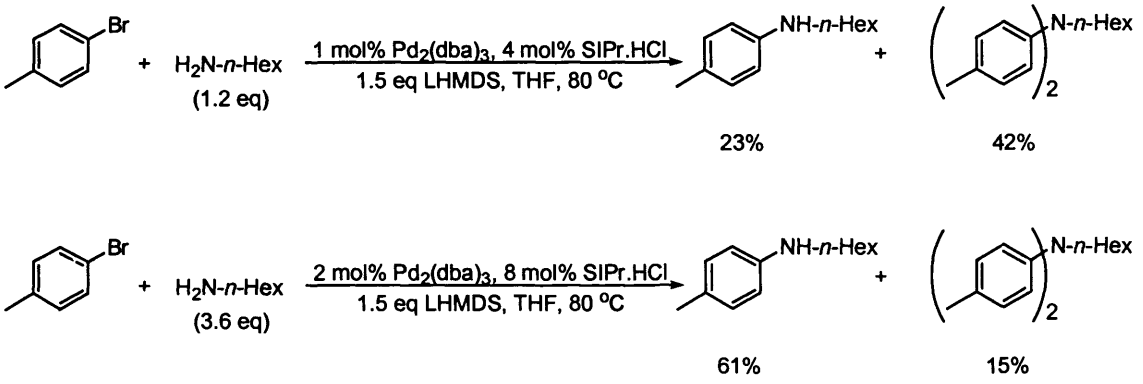
[a]Conditions: Aryl halide (1.0 mmol), amine (1.2 mmol), 1 mol% $Pd_2(dba)_3$, 4 mol% SIPr.HCl, 1.5 eq LHMDS (1 M in THF), 22 °C. All quoted yields are isolated yields. Reaction times were not optimised. [b]3 mol% $Pd_2(dba)_3$, 12 mol% SIPr.HCl. [c]2 mol% $Pd_2(dba)_3$, 8 mol% SIPr.HCl [d]3.6 eq amine, 80 °C, minor bisarylation product also formed in 15% yield.

It was also possible to obtain high yields with short chain secondary acyclic amines like *N*-methylbenzylamine and diethylamine (Table 12, Entries 4-5). However, the longer-chained di-*n*-butylamine required higher catalytic loading even to obtain a low yield of the desired aniline (Table 12, Entry 6). Although amines like di-*n*-butylamine are of similar nucleophilicities to piperidine and morpholine, longer alkyl chains have more degrees of freedom as they are not constrained by a ring system, meaning they are less likely to be in a conformation amenable for reaction and are in possession of greater effective steric bulk.[102]

The reaction of 4-bromotoluene and *n*-hexylamine was tried next. This was an interesting reaction to test, as the coupling of primary amines may be somewhat problematic due to the bisarylation of the amine.[57] This may either be due to the secondary aniline product undergoing further reaction, due to it being a stronger nucleophile than the primary amine starting material, or possibly due to the formation of a catalytically inactive bis(primary amine)palladium(II) complex as reported by Buchwald.[103]

However, bisarylation may be hindered by the addition of extra equivalents of amine,[70] increasing the competition for association to the metal centre: four equivalents have been shown to be sufficient to do this. Bisarylation is also less of a concern when using bulkier primary amine substrates, particularly those branched at the α-postion.[104]

Heating was judged to be needed here for the primary amine *n*-hexylamine to react, as no conversion occurred at room temperature. Unfortunately, bisarylation was the major reaction observed (Scheme 123). However, with higher catalytic loading and an excess of *n*-hexylamine, it was possible to largely hinder this unwanted reaction (Table 12, Entry 7).

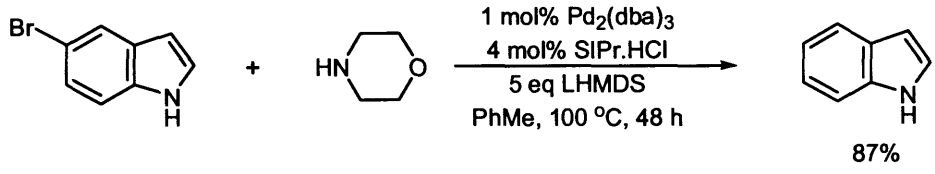


Scheme 123

The effect of the aryl halide was also examined when several reactions were performed with 4-bromoanisole. Although the reactions with this halide were still successful, reactions times were increased and yields reduced, particularly in the case of diethylamine (Table 12, Entries 8-12). This illustrated how electron-donating groups on the aromatic ring will hinder palladium-catalysed reactions.[105]

In order to determine the limitations of this protocol, more elaborate substrates were investigated, beginning with further N-H moieties. Good yields were obtained for the secondary aniline *N*-methylaniline in conjunction with 4-bromotoluene and 4-bromoanisole (Table 12, Entries 16-17). The ability to use this N-H moiety was rather pleasing, as anilines are usually less active in this reaction than alkyl amines due to the resonance afforded by the aromatic ring.[59] However, attempts at coupling the unsubstituted $PhNH_2$ were unsuccessful, even at elevated temperatures, suggesting that only secondary anilines might work in this protocol. Other attempts at broadening the scope of the reaction to include other compounds with an N-H moiety were also unsuccessful: indole, benzophenone hydrazone, *tert*-butylcarbamate and *N,N*-ethylethylenediamine failed to react at both room and elevated temperatures.

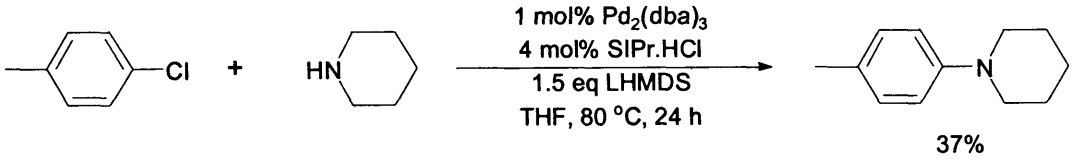
A variety of heteroaryl halides were also examined. The coupling of 2-bromopyridine and piperidine was performed in 73% yield (Table 12, Entry 18), elaborating upon the reported high activity for Pd-NHC catalysts in the amination of halopyridines.[56] However, trials with 2-bromopyrimidine and 5-bromopyrimidine gave no conversion.[106] A range of conditions were examined for 5-bromoindole and morpholine where no reaction took place. However, at 100 °C in toluene with an excess of base, indole was formed in 87% yield as a result of hydrodehalogenation (Scheme 124).[55,57]



Scheme 124

This process was only observed with this substrate, as its product was a solid. It was not observed in other reactions, as the other aryl halides would afford volatile compounds that could not be easily detected, such as benzene, toluene or anisole. As such, it is very likely that this was not the only occasion when hydrodehalogenation actually occurred (e.g. the low-yielding reaction with di-*n*-butylamine), although it would not commonly be the favoured process.[55,57]

The use of aryl chlorides is highly desirable in the Buchwald-Hartwig reaction, as they are more atom efficient and have a lower economic cost in comparison to other aryl halides. A preliminary investigation using 4-chlorotoluene indicated that aryl chlorides would react under this protocol, but with less efficiency than aryl bromides. Even performing the reaction at 80°C failed to achieve more than a modest yield of the desired aniline (Scheme 125).

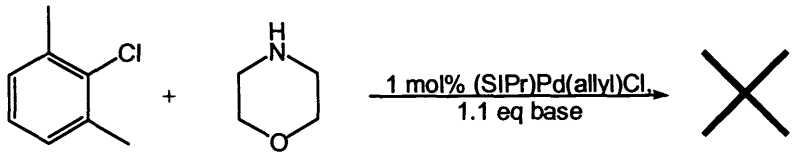


Scheme 125

2.2.5. Evaluation of Study

Despite the significant results obtained using LHMDS as base, it was apparent that the use of imidazolium salt techniques would not suffice for a general protocol. Although high yields could be obtained for several substrates, these conditions did not offer the generality that was required. As such, it was hoped instead that an isolated Pd-NHC complex might offer improvements in activity. The decision was taken to examine (NHC)Pd(R-allyl)Cl complexes, as several sources had cited their activity in coupling reactions, including amine arylation.[41,75-77] For instance, using the (SIPr)Pd(cinnamyl)Cl complex, Nolan had demonstrated the near-quantitative amination of aryl chlorides within one minute (See section 1.3.4.).[41]

However, the scope of substrates that could be used in amine arylation with this class of catalyst had not been fully examined: Nolan's study had only utilised six amines.[41] Additionally, research into (NHC)Pd(R-allyl)Cl complexes had only been conducted with the use of a glovebox, meaning that their potential in a practical organic synthetic procedure had not been considered. This was highlighted by the fact that it was not possible to reproduce one of Nolan's transformations when reagents were weighed out in air and reactions were repeated without a glovebox, either with the unreliable potassium *tert*-butoxide or LHMDS as base (Scheme 126).[41]



i. KO*t*-Bu, DME rt, 16 h
ii. KO*t*-Bu, DME 80 °C, 6 h
iii. LHMDS, THF rt, 6 h
iv. LHMDS, THF 80 °C, 6 h

Nolan's reported result: 1.1 eq KO*t*-Bu, rt, 2.5 h, 95% GC conversion

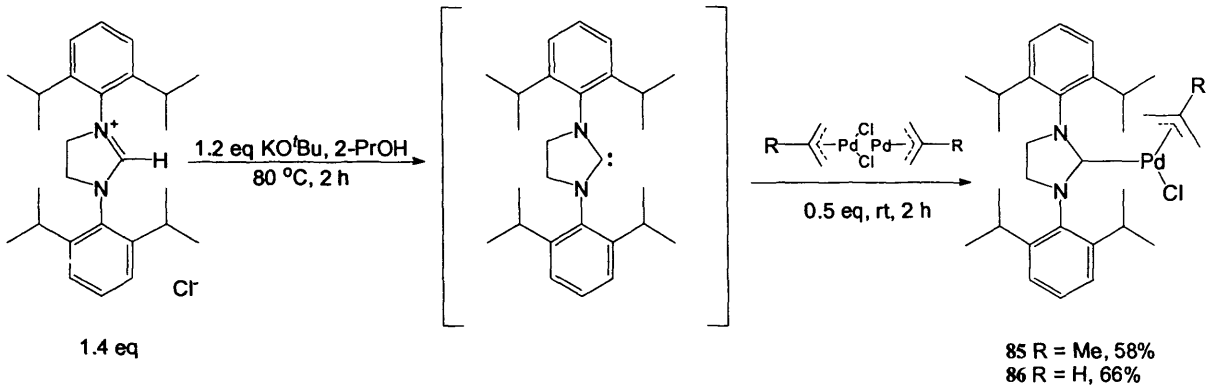
Scheme 126

Nolan had found that substitution on the allyl scaffold would promote the reactions.[41] However, the effects of non-terminal substitution had not been examined at all in amine arylation. Therefore, it was considered whether a complex with the original methallyl scaffold, as in the first complex made in this class ((It-Bu)Pd(methallyl)Cl), would also be active in this reaction.

Rather than re-examining (It-Bu)Pd(methallyl)Cl, with the inefficient It-Bu ligand,[37] the novel (SIPr)Pd(methallyl)Cl **85** was selected for a new study to see whether it could be used for the arylation of a wider range of amines than the imidazolium salt protocol.

2.2.6. Preparation of Isolated Pd-NHC Complexes

As well as (SIPr)Pd(methallyl)Cl **85**, the known complex (SIPr)Pd(allyl)Cl **86** was also selected for the purposes of comparison.[41,42,76,77] Both were prepared using a procedure developed by Nolan consisting of *in situ* formation of the NHC through deprotonation of SIPr.HCl using KO*t*-Bu.[42] This was followed by addition of the relevant $[Pd(R\text{-allyl})Cl]_2$ complex and stirring at ambient temperature to afford the catalyst (Scheme 127). In the case of **86**, it was possible to follow the literature procedure closely, obtaining a pure sample of the complex (as confirmed by elemental and spectral analysis) in a yield of 66% (cf. the literature yield of 82%).[42]



Scheme 127

However, isolation of the novel catalyst **85** required additional effort as spectral analysis of the crude material showed a distinct lack of purity. By following Sigman's example,[77] it was possible to obtain a pure sample of the complex with silica gel chromatography in 58% yield. This illustrated the potential practicality of (NHC)Pd(R-allyl)Cl complexes, as they were demonstrated to be highly inert to manipulation prior to reaction.

2.2.7. Optimisation of (SIPr)Pd(methallyl) Protocol

Optimisation was undertaken using the precatalyst **85** with the aim of achieving yields and reaction times comparable to or better than those afforded by Nolan's glovebox-utilising procedure with the (SIPr)Pd(cinnamyl)Cl complex.[41] Two simple substrates, 2-bromotoluene and morpholine were chosen for this study. Firstly, it was found that when used as purchased, KO*t*-Bu was ineffective as a base in DME with both **85** and **86** (Table 13, Entries 1-2), but that a low yield of the aniline could be obtained in THF with **85** (Table 13, Entry 3). This result could not be improved upon through the use of a commercial 1 M solution of KO*t*-Bu in THF (Table 13, Entry 4).[41] As with the previous imidazolium salt protocol, LHMDS was fundamental to the success of amine arylation, with 1 mol% of **85** leading to complete conversion within thirty minutes (Table 13, Entry 5). This was

a noticeable improvement over typical reaction times in the imidazolium salt study. A repeat run of this reaction showed that the bulk of the amination occurred in the first 10 min. However, as a loading of 1 mol% did not match the literature time and yield,[41] it was necessary to use higher levels of the complex. 3 mol% of (SIPr)Pd(methallyl)Cl sufficiently accelerated the reaction so that it was complete within 1 min in an almost quantitative yield (Table 13, Entry 8).

It was clear that (SIPr)Pd(methallyl)Cl had much more potential to be the catalyst in a general protocol than the *in situ* imidazolium salt techniques. It should also be noted that although reactions were not possible using (SIPr)Pd(allyl)Cl and the alkoxide base, this catalyst was later shown to be more active with LHMDS as base (Table 13, Entry 9).

Table 13: Buchwald-Hartwig reaction of 2-bromotoluene and morpholine using (SIPr)Pd(R-allyl)Cl catalysis.

Entry	Catalyst	Base	Solvent	Time/h	Yield/%
1	1 mol% **85**	KO*t*-Bu	DME	24	-
2	1 mol% **86**	KO*t*-Bu	DME	24	-
3	1 mol% **85**	KO*t*-Bu	THF	6	<5
4[a]	1 mol% **85**	KO*t*-Bu	THF	6	<5
5	1 mol% **85**	LHMDS	THF	0.5	95
6	1 mol% **85**	LHMDS	THF	10 min	82
7	1 mol% **85**	LHMDS	THF	2 min	93
8	1 mol% **85**	LHMDS	THF	1 min	99
9	3 mol% **86**	LHMDS	THF	2 min	89

Conditions: 2-bromotoluene (1.0 mmol), morpholine (1.2 mmol), 1.1 eq base, room temperature. [a]KO*t*-Bu administered as commercial 1 M solution in THF.

Despite the high yield obtained using **85** and LHMDS, the role of the solvent was investigated further, as the choice of THF was largely due to LHMDS being

commercially available as a solution in THF. As one of the key mechanistic steps in the catalytic cycle is thought to be deprotonation of the transmetallation complex,[55] an investigation was undertaken into how solvents with differing effective pH might affect this step and hence the reaction overall. Accordingly, coupling was performed in several different solvents of varying dielectric constant. Only aprotic solvents that would not react with the base were examined.

The arylation of morpholine with the reactive and unhindered 4-bromotoluene was performed in a range of solvents in addition to the preferred THF (Table 14). Only 1 mol% of **85** was employed so that differences in reactivity would be more noticeable. 1,4-Dioxane (like THF, a cyclic ether) was found to afford faster coupling than THF, albeit in a slightly reduced yield. The use of toluene led to an increase in reaction time and a reduction in yield compared to THF and 1,4-dioxane, but a moderate yield was obtained nonetheless.

Table 14 Effect of solvent in the Buchwald-Hartwig reaction of 4-bromotoluene and morpholine

Entry	Solvent	ε_r	Time/min	Yield/%
1	1,4-Dioxane	2.21	10	89
2	Toluene	2.38	60	65
3	Et_2O	4.34	30	50
4	DME	7.2	45	38
5	THF	7.52	20	97
6	DMF	36.7	30	17
7	DMA	37.8	30	-

Conditions: halide (1.0 mmol), morpholine (1.2 mmol), 1 mol% (SIPr)Pd(methallyl)Cl **85**, LHMDS (1.1 mmol), solvent (1.1 mL)

DME has been reported to be the preferred solvent for this reaction when used in conjunction with KO*t*-Bu.[41] However, it was not found to be suitable for this protocol,

affording only a low yield, possibly as it was observed that LHMDS was less soluble in DME than the some of the other solvents tested; this may also explain the moderate yield with diethyl ether. The reaction in DMF only afforded 17% of the aniline product; no coupling product was obtained in DMA. This appeared to show that highly polar solvents are not suitable in this reaction, which was in agreement with a previous study by Kiil,[107] which reported that polar solvents promote β–hydride elimination. Therefore, the conclusion was made that the cyclic ether solvents THF and 1,4-dioxane were the most suitable for use in this reaction out of those tested. The decision was made to continue using THF as the preferred solvent as this afforded the highest yield. The availability of commercial THF solutions of LHMDS also made this a convenient and practical choice.

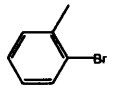
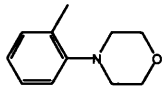
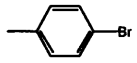
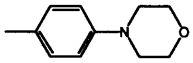
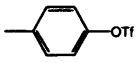
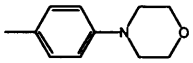
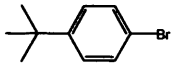
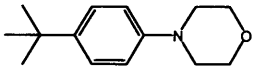
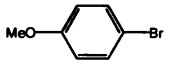
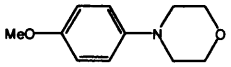
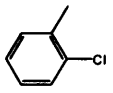
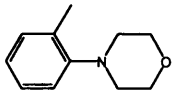
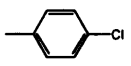
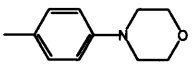
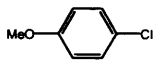
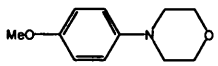
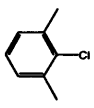
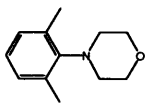
2.2.8. Effect of Aryl Halide in the (SIPr)Pd(methallyl)Cl Protocol.

With optimisation complete, the arylation of morpholine was studied first, as this would allow observations to be made on the facility of oxidative addition for different halides. As with the imidazolium salt study, the reaction of 4-bromotoluene and morpholine was shown to be a particularly facile reaction, with it being complete in near-quantitative yield within 1 min at room temperature (Table 15, Entry 2).

However, it was of concern that in the development of practical protocols for the Buchwald-Hartwig amination, the successful translation of literature protocols into sound and robust organic synthetic procedures has often been difficult, especially for those chemists with less experience in palladium chemistry.

Consequently, the reaction of 4-bromotoluene and morpholine was repeated in a round bottomed flask. An inert atmosphere was generated simply by purging with nitrogen for five minutes prior to the reaction. The reaction proceeded smoothly to give a comparable yield (94%) in a similar reaction time (2 min), indicating the applicability of this procedure. This further enhanced the hopes of developing a general protocol with (SIPr)Pd(methallyl)Cl, by removing the need for expensive specialist glassware.

Table 15: Buchwald-Hartwig reactions of aryl halides and morpholine using (SIPr)Pd(methallyl)Cl **85**

Entry	Halide	Product	Time/mins	Yield/ %
1			1	99
2			1	98
3			1	70
4			5	91
5			5	90
6			25	94
7			5	95
8			10	49
9			60 (10)	24 (52)

Conditions: Aryl halide (1.0 mmol), amine (1.2 mmol), 3 mol% (SIPr)Pd(methallyl)Cl, 1.1 eq LHMDS (1 M in THF), 22 °C. Yields and reaction times in parentheses are for reactions performed at 70 °C.

The ability to perform couplings using aryl triflates is very useful. Aryl triflates may be prepared from phenols, meaning that a triflate may be a more facile leaving group to prepare than bromide or chloride in the presence of other functional groups.[108] *p*-Tolyl triflate was found to react as quickly as 4-bromotoluene, which illustrates the similar reactivity of aryl bromides and triflates in palladium-catalysed reactions. However, the yield with the aryl triflate was slightly lower at only 70% (Table 15, Entry 3).

The presence of *para*-electron-donating groups did not significantly hinder coupling with morpholine (Table 15, Entries 4-5).[105,109] In fact, the exotherm was evident at the start of the reaction (consistent with reports from Nolan)[41] and was most obvious in the case of 4-*tert*-butylbromobenzene.

The reaction of 2-chlorotoluene was also high yielding and rapid (Table 15, Entry 6). This was an interesting result considering the modest yields obtained in the imidazolium salt study. The reaction was even faster with the less hindered 4-chlorotoluene (Table 15, Entry 7). However, the more electron-donating 4-chloroanisole afforded only 49% of the desired aniline (Table 15, Entry 8). As the halide was fully consumed, it would appear that the low yield was due to the greater prevalence of β–hydride elimination when using deactivated halides.[105,109] The highly hindered 2,6-dimethylchlorobenzene yielded only 24% of the desired aniline. However, the yield was raised to 52% by performing the reaction at 70 °C rather than room temperature. (Table 15, Entry 9).

2.2.9. Effects of Secondary Amines in the (SIPr)Pd(methallyl)Cl Protocol.

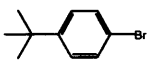
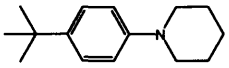
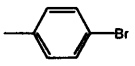
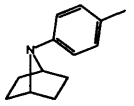
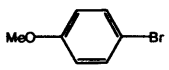
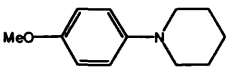
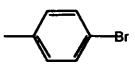
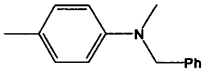
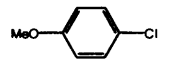
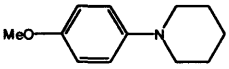
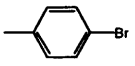
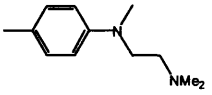
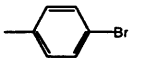
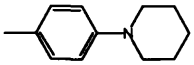
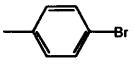
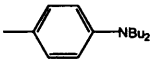
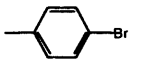
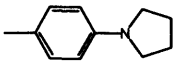
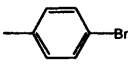
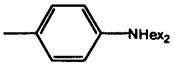
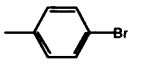
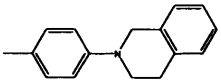
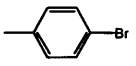
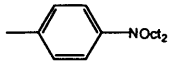
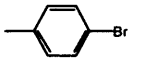
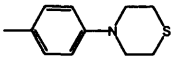
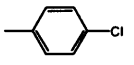
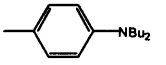
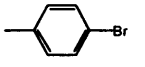
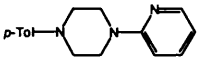
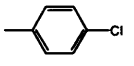
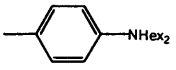
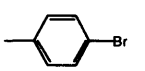
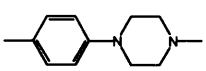
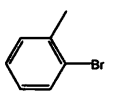
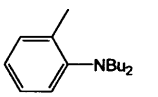
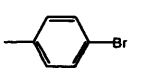
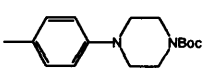
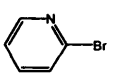
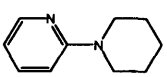
With investigations into the aryl halide component complete, the study advanced onto examining the scope of other amines. Firstly, the high reactivity of secondary cyclic amines was shown with piperidine, although again only a moderate yield of 43% was obtained for the deactivated 4-chloroanisole (Table 16, Entry 3).

Having tested a wide range of halides, the decision was then taken to keep the aryl halide component constant and to vary the amine, so that the effect of the amine could be highlighted. 4-Bromotoluene was selected for this role due to it being unhindered and relatively electronically neutral.

Whilst similar in structure to piperidine, pyrrolidine was shown to be less reactive, as at room temperature, full consumption of the halide did not occur. Repeated trials showed that no further reaction took place after approximately 5 min. However, by heating at 70 °C, full consumption of the halide occurred within 2 min in a high yield (Table 16, Entry 5). The drug moiety 1,2,3,4-tetrahydroisoquinoline[110] was found to undergo arylation with 4-bromotoluene in 65% yield at room temperature (Table 16, Entry 6). Thiomorpholine was shown to couple with a reduced yield (*cf.* morpholine (Table 15, Entry 2)) of 60% (Table 16, Entry 7). This was nonetheless an important result, as it showed that the (SIPr)Pd(methallyl)Cl precatalyst would enable the reactions of sulfur-containing reagents, which are traditionally viewed as poisons to palladium catalysts.[111] 1-(2-pyridiyl)-piperazine also coupled rapidly and in a high yield despite the lone pair on the pyridyl ring (Table 16, Entry 8). High yields were also obtained with further *N*-substituted piperazines (Table 16, Entries 9-10).

The bicyclic amine 7-azabicyclo[2.2.1]heptane hydrochloride failed to react at room temperature, although 9% yield was obtained at 70 °C. Although the amine was administered in this reaction as the hydrochloride salt, extra equivalents of LHMDS were utilised to compensate for this. Thus the low yield here may instead be attributed to the steric bulk of the amine.

Table 16: Buchwald-Hartwig reactions of aryl halides and other secondary amines using (SIPr)Pd(methallyl)Cl **85**

Entry	Halide	Product	Time/ mins	Yield/ %	Entry	Halide	Product	Time/ mins	Yield/ %
1			20	82	11[b]			16h (3h)	- (9)
2			20	93	12			5	83
3			15	43	13			18 (5h)	38[a] (85)
4			5	85	14			18h (60)	42[a] (86)
5			5 (2)	40[a] (84)	15			24h (60)	- (98)
6			30	65	16			24h (60)	- (82)
7			10	60	17			(30)	(10)
8			5	96	18			(30)	(25)
9			5	80	19			24h (90)	- (21)
10			5	96	20			1	91

Conditions: Aryl halide (1.0 mmol), amine (1.2 mmol), 3 mol% (SIPr)Pd(methallyl)Cl, 1.1 eq LHMDS (1 M in THF), 22 °C. Yields and reaction times in parentheses are for reactions performed at 70 °C. [a]Reaction would not go to completion. [b]Amine used as hydrochloride salt with 2.4 eq LHMDS

Owing to the limited success in the coupling of secondary acyclic amines in the earlier imidazolium salt study, they were re-examined using (SIPr)Pd(methallyl)Cl.

Although the shorter-chain *N*-methylbenzylamine coupled rapidly in 83% yield, the corresponding reaction with *N,N,N'*-trimethyl-1,2-diaminoethane failed to proceed to completion at room temperature, but this was rectified by heating at 70 °C (Table 16, Entries 12-13). However, it is possible that the lone pair on the tertiary amine motif may also have hindered this reaction by ligation to the palladium species.

Symmetrical acyclic secondary amines were also tested. The room temperature reaction of 4-bromotoluene and di-*n*-butylamine only afforded 42% of the coupling product and would not proceed to completion. Di-*n*-hexylamine and di-*n*-octylamine failed to react at all at room temperature. However, when heated at 70 °C, all three acyclic amines fully reacted within one hour in high yields (Table 16, Entries 14-16). The reactions of 4-chlorotoluene with di-*n*-butylamine and di-*n*-hexylamine were rapid, but poor yielding at 70 °C (Table 16, Entries 17-18). As the halide was fully consumed in these examples, it can be deduced that this was due to hydrodehalogenation.[109] Attempts at the arylation of di-*n*-butylamine with the more hindered 2-bromotoluene showed that this would not react at all at room temperature and that heating was a necessity, even in order to obtain a low yield of 21%.

Finally, it was demonstrated that heteroaryl halides would react under these conditions: 2-bromopyridine was coupled with piperidine in a high yield within 1 min at room temperature, showing that the lone pair of the nitrogen on the pyridyl ring had little effect on the activity of the new catalyst (Table 16, Entry 20).[56]

Not all attempted reactions of secondary alkyl amines were successful. The hindered *N*-methyl-*tert*-butylamine, *N*-(tetrahydropyran-4-yl)methylamine and *cis*-2,6-dimethylpiperidine all failed to react, either at room temperature or at 70 °C. It is likely that they were too sterically hindered for the N-H moiety to be able to reach the palladium centre in the transmetallation step.[53,55] The latter was a clear example of how apparently modest increases in steric bulk may have dramatic effects on the success of amine arylation.

2.2.10. Effects of Primary Amines in the (SIPr)Pd(methallyl)Cl Protocol.

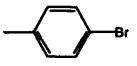
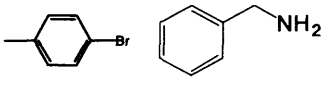
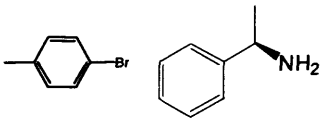
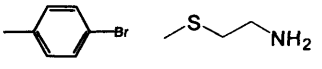
With a range of secondary amines exemplified, the reactions of primary amines were examined next. In the reaction of 4-bromotoluene with four equivalents of *n*-hexylamine, the halide was consumed within one hour in THF at 70 °C affording 64% yield of the desired product (as with the SIPr.HCl study, heating was deemed to be necessary with primary amines). However, bisarylation was still observed, albeit in only 12% yield (Table 17, Entry 1). Despite similar yields with $Pd_2(dba)_3$ and SIPr.HCl, this was still a significant result which showed the increased activity of the (SIPr)Pd(methallyl)Cl pre-catalyst, as the reaction was complete much more rapidly.

Under the same conditions, the reactions of 4-bromotoluene with benzylamine and (*R*)-(+)-1-phenylethylamine proceeded selectively with no bisarylation being observed, with yields of 45% and 70% obtained respectively (Table 17, Entries 2-3). The selectivity here was attributed to the greater steric bulk of these amines, which it is believed prevented further reaction.[107]

The sulfur-containing amine 2-(methylthio)ethylamine was also found to undergo arylation (Table 17, Entry 4). While this reaction only afforded 14% yield of the desired product, the bisarylation product was not observed. Despite the modest yield, this was another key reaction, further showing that sulfur-containing substrates could be utilised under this protocol.

Despite increasing selectivity, greater steric bulk also proved to be problematic in some cases, as the highly bulky amines *tert*-butylamine and adamantylamine failed to react altogether. In the case of *tert*-butylamine (bp: 46 °C), it was a concern that the reaction was performed above its boiling point. However, arylation also failed to occur at 40 °C.

Table 17: Buchwald-Hartwig reactions of aryl halides and primary amines and anilines using (SIPr)Pd(methallyl)Cl **85**.

Entry	Halide	Amine	Time/ mins	Yield/ % ArNHR	Yield/ % Ar_2NR
1		*n*-HexNH_2	60	64	12
2			30	45	-
3			30	70	-
4			60	14	-

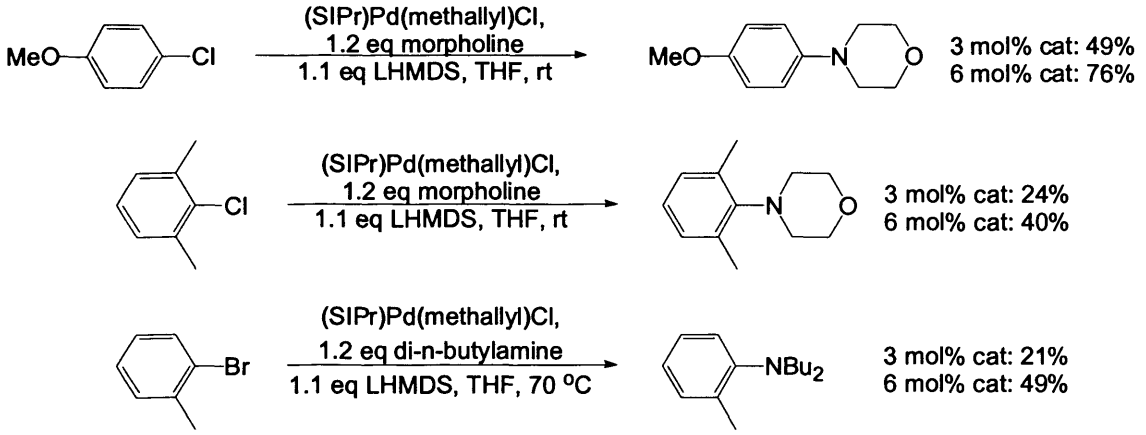
Conditions: Aryl halide (1.0 mmol), amine (4.0 mmol, 4.0 eq), 3 mol% (SIPr)Pd(methallyl)Cl, 1.1 eq LHMDS (1M in THF), 70 °C.

2.2.11. Promoting Reactions *via* Increased Catalyst Loading

In the optimisation process, the benefits of higher catalytic loading were illustrated through higher yields and decreasing reaction times. Although 3 mol% (SIPr)Pd(methallyl)Cl was effective with the more reactive substrates, when dealing with highly bulky substrates or deactivated aryl chlorides, it was insufficient.

For these cases, it was determined that higher catalyst loading was a potential remedy.[41] Although this sounded like an unattractive prospect, it was nonetheless more facile than the lengthy and laborious dropwise addition of the halide.

Higher catalyst loading promoted the room temperature coupling of the deactivated 4-chloroanisole and the highly bulky 2,6-dimethylchlorobenzene with morpholine (Scheme 128). This also enhanced the yield in the reaction of 2-bromotoluene and di-*n*-butylamine.



Scheme 128

The fact that this reaction failed at room temperature (Table 16, Entry 19) helped to highlight the approach that must be taken when dealing with less reactive chemicals. Should a novel reaction not proceed at room temperature, both heating and increased catalyst loading are likely to improve results. Of course, to avoid the need for repeated

trials, it may instead be more facile to simply heat the reaction and employ higher levels of the catalyst (>6 mol%), within reason, at the earliest opportunity.

2.2.12. Conclusions

Most studies on amine arylation have concentrated on showing how novel catalysts will improve reaction times and yields for a familiar array of common substrates. Here, efforts have been made to examine the possibility of the convenient SIPr.HCl imidazolium salt or the (SIPr)Pd(methallyl)Cl complex being used as the catalysts in a general protocol.

Although a truly general protocol was not achieved, it was demonstrated that significant advances in the Buchwald-Hartwig reaction were possible, especially with the use of (SIPr)Pd(methallyl)Cl and LHMDS. With suitable catalytic loading and/or heating, they will effect the coupling of a wide range of aryl halides with primary and secondary alkyl amines, although difficulties may be encountered when utilising highly bulky substrates.

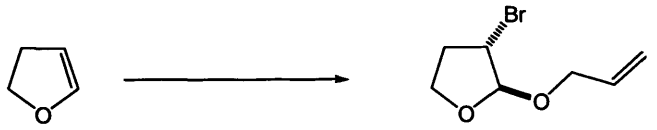
Future studies from within the Caddick laboratories will now concentrate on attempts at extending the scope of molecules with an N-H moiety that will undergo arylation in the presence of (SIPr)Pd(methallyl)Cl. Further advances towards the aim of a general protocol are also likely to be forthcoming with the development of new Pd-NHC catalysts, which it is hoped will offer even higher activity than (SIPr)Pd(methallyl)Cl.

3. Experimental Section

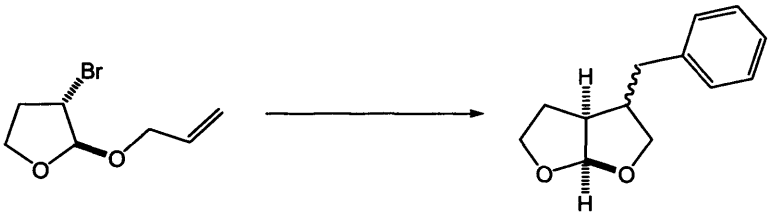
General information: All chemicals were purchased from commercial sources, except for *N*-(tetrahydropyran-4-yl)methylamine, *N,N,N'*-trimethyl-1,2-diaminoethane and 7-azabicyclo[2.2.1]heptane hydrochloride, which were supplied by AstraZeneca Pharmaceuticals. If liquid, aryl halides and amines were distilled over potassium hydroxide and stored over molecular sieves prior to use. All other chemicals were used as received without further purification. Unless otherwise stated, all reactions were carried out under an atmosphere of either nitrogen or argon. Reaction solvents were either HPLC grade or were dried over alumina pellet columns, manufactured by Anhydrous Engineering USA. The reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254 mm). Flash column chromatography was carried out with Kieselgel 60 M 0.04/0.063 mm (230-400 mesh) silica gel. All yields quoted are isolated yields. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz on a Bruker AMX 300. Other ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz on a Bruker AMX 400 at ambient temperature in $CDCl_3$ (unless otherwise stated). The chemical shifts (δ) for ^{1}H and ^{13}C are quoted in ppm relative to residual protiated signals of the solvent. Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Shimadzu FTIR 8700 Spectrophotometer. Elemental analyses for novel compounds were performed at the Department of Chemistry, University College London. Melting points were measured with a Gallenkamp apparatus and are uncorrected.

3.1. Studies into Transition-Metal Mediated Heterocycle Formation

3.1.1. Preliminary Study

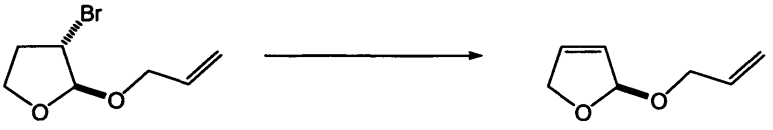


3-Bromo-2-allyloxytetrahydrofuran (25).[85] 2,3-Dihydrofuran (756 μL, 10 mmol) and allyl alcohol (1.4 mL, 20 mmol, 2.0 eq) were dissolved in dichloromethane (200 mL) and cooled to 0 °C. *N*-Bromosuccinimide (1.96 g, 11 mmol, 1.1 eq) was slowly added to the reaction medium and the mixture was stirred at ambient temperature overnight. The solvent was removed *in vacuo* and the crude residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:19) to afford the title compound as a colourless oil (0.81 g, 3.9 mmol, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07-2.28 (m, 1H, C*H*$_2$), 2.54-2.77 (m, 1H, C*H*$_2$), 3.88-4.30 (m, 5H, C*H*Br, OC*H*$_2$, OC*H*$_2$CH=CH$_2$), 5.15-5.32 (m, 2H, =C*H*$_2$), 5.24 (s, 1H, OC*H*O), 5.79-5.96 (m, 1H, C*H*=). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.9, 50.0, 66.8, 68.1, 108.0, 117.4, 134.0.



(3*R, 3a*S**, 6a*R**)-Benzylhexahydrofuro[2,3-*b*]furan (26b).**[23] Nickel iodide (38 mg, 0.12 mmol, 0.06 eq), *trans*-2-aminocyclohexanol hydrochloride (18 mg, 0.12 mmol, 0.06 eq), sodium hexamethyldisilazide (0.73 g, 4.0 mmol, 2.0 eq) and phenylboronic acid (293 mg, 2.4 mmol, 1.2 eq) were placed together in a Schlenk tube with a magnetic stirrer. The flask was sealed, cycled with nitrogen/vacuum three

times, and 2-propanol (4 mL) was added slowly. After stirring for 5 min at room temperature, 3-bromo-2-allyloxytetrahydrofuran (409 mg, 2.0 mmol, 1.0 eq) was added in 2-propanol (1 mL) and stirring continued at 60 °C for 6 h. The mixture was then cooled to room temperature, after which it was diluted with dichloromethane (100 mL) and filtered through a short pad of silica. The solvent was removed *in vacuo* and the crude residue purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:4) to afford the title compound as a yellow/brown oil (247 mg, 1.2 mmol, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84-1.92 (m, 1H), 1.93-2.07 (m, 1H), 2.57-2.84 (m, 4H), 3.52-3.60 (m, 2H), 3.81-3.91 (m, 2H), 3.91-4.00 (m, 1H), 5.71 (d, J = 4.8 Hz, 1H, OC*H*O), 7.13-7.34 (m, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 33.8, 43.8, 45.5, 69.1, 72.2, 109.8, 126.3, 128.4, 128.6, 140.0. EI MS (relative intensity): 204 (M^+, 40), 186 (48), 173 (8), 160 (30), 142 (77), 129 (52), 117 (97), 104 (74), 91 (100). HRMS EI [M^+], Calcd.: 204.11502. Actual: 204.11448. IR (KBr, cm^{-1}): 3084, 3060, 3026, 2949, 2864, 1602, 1494, 1454, 1369, 1280, 1251, 1205, 1186, 1110, 1078, 1064, 1012, 958, 943, 921, 891, 748, 702.

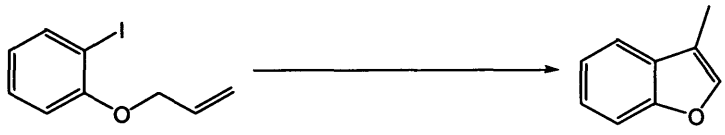


2-Allyloxy-2,5-dihydrofuran (51). Nickel iodide (38 mg, 0.12 mmol, 0.06 eq), *trans*-2-aminocyclohexanol hydrochloride (18 mg, 0.12 mmol, 0.06 eq) and sodium hexamethyldisilazide (0.73 g, 4.0 mmol, 2.0 eq) were placed together in a Schlenk tube with a magnetic stirrer. The flask was sealed, cycled with nitrogen/vacuum three times and 2-propanol (4 mL) was added. It was stirred for 5 min at room temperature, after which 2-allyloxytetrahydrofuran (409 mg, 2.0 mmol, 1.0 eq) in 2-propanol (1 mL) was added and stirring was continued at 60 °C for 48 h. The mixture was then

cooled to room temperature, diluted with dichloromethane (100 mL) and filtered through a short pad of silica. The solvent was removed *in vacuo* and the crude residue purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:9) to afford the title compound as a colourless oil (91 mg, 0.72 mmol, 36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (m, 2H), 4.52 (dddd, J = 14.0 Hz, 2.4 Hz, 1.7 Hz, 1.2 Hz, 1H), 4.69 (dddd, J = 14.0 Hz, 4.3 Hz, 2.6 Hz, 1.5 Hz, 1H), 5.13 (ddt, J = 10.3 Hz, 1.70 Hz, 1.3 Hz, 1H), 5.25 (ddd, J = 17.2 Hz, 3.3 Hz, 1.6 Hz, 1H), 5.78 (ddt, J = 6.1 Hz, 2.5 Hz, 2.5 Hz, 1.1 Hz, 1H), 5.82-5.88 (m, 1H), 5.88-5.98 (m, 3H), 6.22 (ddd, J = 6.0 Hz, 2.8 Hz, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.0 (CH_2), 74.4 (CH_2), 108.1 (CH), 116.9 (CH_2), 125.9 (CH), 132.1 (CH), 134.7 (CH). E.S.I. MS (relative intensity): 167 (12), 149 (40), 136 (15), 127 (M^++H, 17), 126 (M^+, 11), 125 (M^+-H, 22), 111 (43), 97 (84), 83 (100). IR (KBr, cm^{-1}): 3028, 2923, 2852, 1633, 1454, 1384, 1276, 1049, 750, 698, 607.

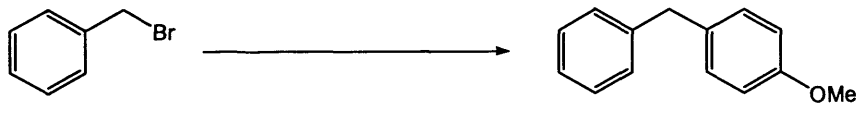
(2-Iodophenyl)-3-allylether (52).[111] 2-iodophenol (1.5 g, 6.8 mmol), sodium iodide (0.3 g, 1.7 mmol, 0.25 eq), allyl bromide (0.82 g, 6.8 mmol, 1.0 eq) and potassium carbonate (1.9 g, 13.0 mmol, 1.91 eq) were added to reagent grade acetone (40 mL) and heated under reflux for 6 h. The mixture was cooled to room temperature and filtered through celite. The solvent was removed under reduced pressure and the crude residue was taken up in ether (40 mL): this was washed with water (2 x 20 mL). The aqueous extracts were combined and extracted with ether. The combined organic extracts were dried over magnesium sulfate, after which the solvent was removed under reduced pressure. The crude material was purified *via* flash column

chromatography (silica gel) using an eluent of diethyl ether/petroleum ether (1:9) to afford the title compound as a colourless oil (1.31 g, 5.1 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (d, J = 4.8 Hz, 2H, OCH_2), 5.32 (d, J = 10.6 Hz, 1H, $CH=CH_2$), 5.52 (d, J = 17.3 Hz, 1H, $CH=CH_2$), 6.02-6.11 (m, 1H, $CH=CH_2$), 6.72 (t, J = 7.8 Hz, 1H, Ar), 6.81 (d, J = 7.8 Hz, 1H, Ar), 7.28 (t, J = 7.8 Hz, 1H, Ar), 7.78 (d, J = 7.8 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.7, 86.7, 112.5, 117.6, 122.7, 129.4, 132.6, 139.6, 157.1. EI MS (relative intensity): 260 (M^++1, 100), 220 (12), 191 (17), 171 (11), 149 (11), 133 (29), 119 (8), 105 (43), 92 (43). HRMS E.I. [M^+], Calcd.: 259.9691. Actual: 259.96965.



3-Methylbenzo[*b*]furan (53).[111] An oven-dried Schlenk tube was charged with (2-iodophenyl)-3-allylether (0.19 g, 0.74 mmol), caesium carbonate (0.36 g, 1.10 mmol, 1.5 eq), $Pd_2(dba)_3$ (0.0068 g, 0.01 eq), 1,3-bis-(2,4,6-trimethylphenyl)imidazolinium chloride (0.0025 g, 0.01 eq) and a magnetic stirrer bar. The flask was cycled with argon/vacuum three times, after which *N,N*-dimethylacetamide (10 mL) was added. The flask was stirred at 140 °C. After 1.5 h, when all starting material had been consumed as judged by TLC, the mixture was cooled to room temperature and filtered through celite. The filtrate was washed with water (2 x 15 mL) and the aqueous extracts were combined and extracted with ether (4 x 25 mL). The combined organic extracts were dried over magnesium sulfate, after which the solvent was removed *in vacuo*. The crude material was purified *via* flash chromatography (silica gel) using an eluent of diethyl ether/petroleum ether (1:9) to afford the title compound as a colourless oil (70 mg, 0.52 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (d, J =

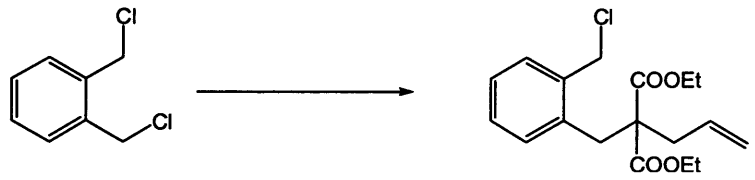
1.3 Hz, 3H, CH_3), 7.24-7.30 (m, 2H, Ar), 7.44-7.47 (m, 1H, Ar), 7.52-7.55 (m, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 7.9, 111.3, 115.6, 119.4, 122.2, 124.1, 129.3, 141.3, 155.2. E.I. MS (relative intensity): 135 (100), 133 (M^++H, 92), 131 (77), 121 (35), 113 (37), 107 (82), 97 (45), 91 (38), 85 (50). HRMS E.I. [M^++H], Calcd.: 133.06534. Actual: 133.06495. IR (KBr, cm^{-1}): 2922, 2855, 1672, 1634, 1597, 1456, 1375, 1258, 1094, 1024, 961, 800, 746.



4-Benzylanisole (54). An oven-dried Schlenk tube was charged with benzyl bromide (171 mg, 1.0 mmol), 4-methoxyphenylboronic acid (231 mg, 1.5 mmol, 1.5 eq), $Pd_2(dba)_3$ (23 mg, 0.025 mmol, 0.05 eq Pd), di-*tert*-butylmethylphosphonium tetrafluoroborate (25 mg, 0.10 mmol, 0.10 eq) and a magnetic stirrer. It was sealed with a septum and cycled with nitrogen/vacuum three times. 1,4-Dioxane (5 mL) was added *via* syringe and the mixture was stirred at room temperature for 24 h. The mixture was then diluted with diethyl ether, filtered through a sintered funnel and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of diethyl ether/petroleum ether (1:9) to afford the title compound as a colourless oil (143 mg, 0.72 mmol, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H, OCH_3), 4.00 (s, 2H, PhCH_2), 6.90-6.92 (m, 2H, Ar), 7.17-7.20 (m, 2H, Ar), 7.24-7.28 (m, 3H, Ar), 7.33-7.38 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.1, 55.3, 114.0, 126.1, 128.5, 128.9, 130.0, 133.3, 141.7, 158.1. E.I. MS (relative intensity): 214 (29), 198 (M^+, 100), 180 (30), 167 (37), 153 (19), 121 (28), 103 (25), 91 (45). HRMS EI [M^+], Calcd.: 198.10392. Actual: 198.10330.

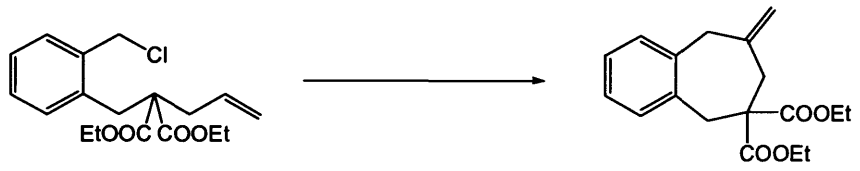
4-Benzylanisole (54). An oven-dried Schlenk tube was charged with benzyl chloride (127 mg, 1.0 mmol), 4-methoxyphenylbornic acid (231 mg, 1.5 mmol, 1.5 eq), $Pd_2(dba)_3$ (23 mg, 0.025 mmol, 0.05 eq Pd), di-*tert*-butylmethylphosphonium tetrafluoroborate (25 mg, 0.10 mmol, 0.10 eq) and a magnetic stirrer. It was sealed with a septum and cycled with nitrogen/vacuum three times. 1,4-Dioxane (5 mL) was added *via* syringe and the mixture was stirred at room temperature for 24 h. The mixture was then diluted with diethyl ether, filtered through a sintered funnel and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of diethyl ether/petroleum ether (1:9) to afford the title compound as a colourless oil (108 mg, 0.55 mmol, 55%). Spectral data as above.

3.1.2. Preparation of 8-Methylene-5,7,8,9-tetrahydrobenzocycloheptene-6,6-dicarboxylic acid diethyl ester (56).



(2-Chloromethylbenzyl)malonic acid diethyl ester (55).[10] Sodium hydride (1.46 g, 60% suspension in mineral oil, 36.4 mmol) was suspended in tetrahydrofuran (40 mL). At room temperature, diethyl allylmalonate (6.62 g, 31.5 mmol) was added dropwise. Once effervescence of hydrogen had stopped, this was allowed to stir for 30 min, after which α,α'-dichloro-*o*-xylene (7.4 g, 21.5 mmol) in tetrahydrofuran (20 mL) was added. Stirring continued for 5 h, at which time TLC showed the reaction to

be complete. The mixture was diluted with ethyl acetate (200 mL) and quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (200 mL) and water (200 mL). After drying over magnesium sulfate, the solvent was removed *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of dichloromethane to afford the title compound as a colourless oil (6.5 g, 19 mmol, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.2 Hz, 6H, OCH_2CH_3), 2.69 (d, J = 7.2 Hz, 2H, $CH_2CH{=}CH_2$), 3.41 (s, 2H, $ArCH_2C$), 3.99-4.25 (m, 4H, OCH_2), 4.65 (s, 2H, $ArCH_2Cl$), 5.07-5.19 (m, 2H, $=CH_2$), 5.67-5.86 (m, 1H, $CH{=}$), 7.20-7.25 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 33.9, 38.4, 44.4, 58.8, 61.4, 119.4, 127.4, 128.6, 130.6, 130.8, 132.5, 135.4, 136.8, 170.9. C.I. MS (relative intensity): 339 (M^++H, 100), 303 (100), 257 (45), 229 (34), 199 (10), 183 (16), 155 (28). HRMS CI [M^++H], Calcd.: 339.13630. Actual: 339.13525. IR (KBr, cm^{-1}): 2981, 2937, 2906, 1732, 1641, 1494, 1465, 1444, 1390, 1367, 1332, 1197, 1139, 1097, 1035, 1014, 923, 862, 769, 732, 673.

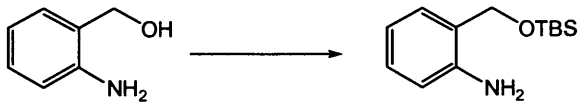


8-Methylene-5,7,8,9-tetrahydrobenzocycloheptene-6,6-dicarboxylic acid diethyl ester (56).[10] A microwave vial was charged with 2,2-(2-chloromethylbenzyl)-allyl-diethylmalonate (68 mg, 0.2 mmol) and dichlorobis(triphenylphosphine)palladium(II) (7 mg, 0.01 mmol, 0.05 eq). Acetonitrile (1.5 mL) was added next, followed by *N,N*-dicyclohexylmethylamine (86 μL, 0.4 mmol, 2.0 eq). This mixture was heated in a microwave reactor at 90 °C for 20 min. The crude residue was diluted with

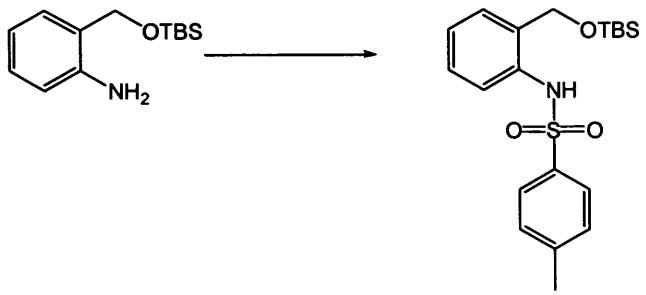
dichloromethane (5 mL) and immediately placed onto a column for silica gel chromatography in dichloromethane/petroleum ether (1:1) to afford the title compound as a colourless oil (57 mg, 0.19 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.0 Hz, 6H, OCH_2CH_3), 2.78 (s, 2H, C7 CH_2), 3.37 (s, 2H, $ArCH_2$), 3.55 (s, 2H, $ArCH_2$), 4.14 (q, J = 7.0 Hz, 4H, OCH_2), 4.92 (s, 1H, $=CH_2$), 4.96 (s, 1H, $=CH_2$), 7.06-7.14 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 38.1, 41.8, 42.2. 56.7, 61.4, 114.6, 126.4, 127.4, 128.4, 135.3, 139.5, 141.5, 170.8. E.I. MS (relative intensity): 302 (M^+, 18), 228 (35), 199 (55), 155 (100), 142 (14), 128 (16), 115 (11). HRMS E.I. [M^+], Calcd.: 302.1126. Actual: 302.15084. IR (KBr, cm^{-1}): 2979, 2937, 2906, 1732, 1681, 1645, 1492, 1454, 1386, 1367, 1325, 1298, 1263, 1236, 1199, 1180, 1159, 1124, 1095, 1053, 1014, 891, 748.

8-Methylene-5,7,8,9-tetrahydrobenzocycloheptene-6,6-dicarboxylic acid diethyl ester (56).[10] A microwave vial was charged with 2,2-(2-chloromethylbenzyl)-allyl-diethylmalonate (68 mg, 0.2 mmol) and dichlorobis(triphenylphosphine)palladium(II) (7 mg, 0.01 mmol, 0.05 eq). Acetonitrile (1.5 mL) was added next, followed by triethylamine (56 μL, 0.4 mmol, 2.0 eq). This mixture was heated in a microwave reactor at 90 °C for 20 min. The crude residue was diluted with dichloromethane (5 mL) and immediately placed onto a column for silica gel chromatography in dichloromethane/petrol (1:1) to afford the title compound as a colourless oil (37 mg, 0.12 mmol, 63%). Spectral data as above. The unreacted starting material 2,2-(2-chloromethylbenzyl)-allyldiethylmalonate (**55**) was also recovered as a colourless oil (16 mg, 0.05 mmol, 23%).

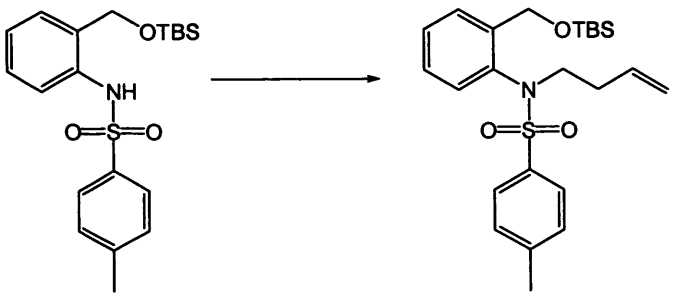
3.1.3. Preparation of (N-Tosyl)-4-methylene-2,3,4,5-tetrahydrobenzazepine (69).



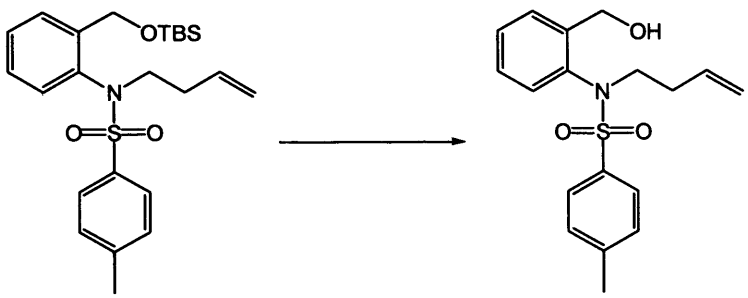
2-Aminobenzyl-*tert*-butyldimethylsilyl ether (58a). 2-aminobenzyl alcohol (7.4 g, 60 mmol) was dissolved in dry *N,N*-dimethylformamide (100 mL). Imidazole (10.2 g, 150 mmol, 2.5 eq) and *tert*-butyldimethysilyl chloride (9.9 g, 66 mmol, 1.1 eq) were added and the mixture was allowed to stir at room temperature for 15 h. At this time, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic extracts were washed with brine (100 mL) and water (100 mL), after which they were dried over magnesium sulfate. The solvent was removed *in vacuo*. The title compound was isolated as a brown oil without further purification (14.2 g, 59.9 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 6H, SiMe), 0.83 (s, 9H, *t*-Bu), 4.10 (br, 2H, NH_2), 4.61 (s, 2H, CH_2O), 6.62 (dd, J = 7.6 Hz, 6.6 Hz, 2H, Ar), 6.96 (d, J = 7.0 Hz, 1H, Ar), 7.02 (t, J = 7.6 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.23, 18.2, 25.9, 65.0, 115.7, 117.9, 125.3, 128.5, 128.7, 146.2. C.I. MS (relative intensity): 238 (M^++H, 20), 211 (28), 180 (72), 161 (17), 134 (27), 106 (100). HRMS CI [M^++H], Calcd.: 238.16271. Actual: 238.16219.



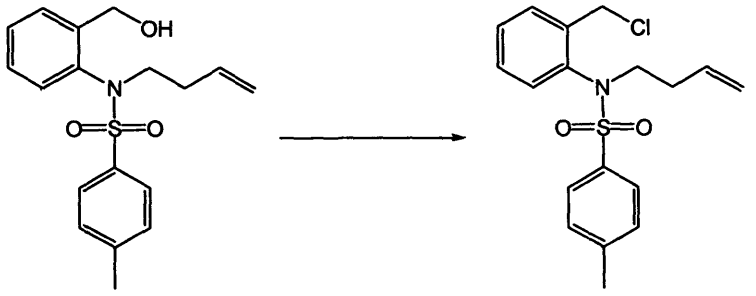
2-(*N*-tosylamino)benzyl-*tert*-butyldimethylsilyl ether (58b).[90] 2-aminobenzyl-*tert*-butyldimethylsilyl ether (5.9 g, 25 mmol) was dissolved in dry dichloromethane (90 mL) with triethylamine (21 mL, 150 mmol, 6.0 eq). The solution was cooled to 0 °C and *para*-toluenesulfonyl chloride (5.7 g, 30 mmol, 1.0 eq) in dichloromethane was added dropwise. The reaction mixture was allowed to stir at room temperature for 24 h. The solution was then poured into water (250 mL) and the product was extracted with dichloromethane (3 x 200 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was triturated with hexane to remove the soluble unreacted amine impurity. The crude solid residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:9). The title compound was afforded as a white crystalline solid (mp: 128 °C, 5.3 g, 13.5 mmol, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H, SiMe), 0.95 (s, 9H, Si-^{t}Bu), 2.34 (s, 3H, SO_2PhCH_3), 4.37 (s, 1H, $ArCH_2O$), 6.89-7.08 (m, 2H, Ar), 7.16-7.28 (m, 3H, Ar), 7.53 (dd, J = 8.2 Hz, 0.8 Hz, 1H, Ar), 7.64 (d, J = 8.2 Hz, 2H, Ar), 8.33 (s, 1H, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.5, 18.2, 21.5, 25.8, 65.1, 122.3, 124.5, 127.0, 127.9, 128.8, 129.6, 130.6, 137.0. FAB+ MS (relative intensity): 436 (12), 414 (M^++Na, 100), 390 (5), 334 (18), 261 (8), 237 (2), 197 (15). HRMS FAB [M^++Na], Calcd.: 414.15350. Actual: 414.15403. IR (KBr, cm^{-1}): 2954, 2929, 2858, 1633, 1539, 1494, 1461, 1392, 1338, 1305, 1257, 1232, 1164, 1107, 1091, 1058, 1039, 1004, 925, 833, 812, 779, 754, 661, 565, 547.



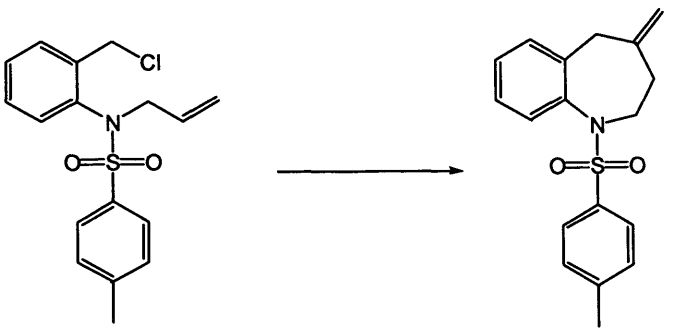
2-(*N,N*-homoallyltosylamino)benzyl-*tert*-butyldimethylsilyl ether (59). A solution containing 2-(*N*-tosylamino)benzyl-*tert*-butyldimethylsilyl ether (1.68 g, 4.23 mmol) and homoallyl bromide (0.66 mL, 6.45 mmol) in acetone (30 mL) was heated under reflux overnight in the presence of potassium carbonate (712 mg, 5.16 mmol). The reaction medium was then diluted with water and extracted with ether (3 x 150 mL). The combined organic extracts were washed with water (200 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to afford the title compound without further purification as a colourless oil (1.9 g, 4.26 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (d, J = 4.6 Hz, 6H, SiMe), 0.96 (s, Si*t*-Bu, 9H), 1.99-2.35 (m, 2H, NCH_2CH_2), 2.44 (s, 3H, ArMe), 3.00-3.32 (m, 1H, NCH_2), 3.67-3.99 (m, 1H, NCH_2), 4.92 (s, 2H, $ArCH_2O$), 4.99 (t, J = 1.4 Hz, 1H, $=CH_2$), 5.00-5.07 (m, 1H, $=CH_2$), 5.59-5.77 (m, 1H, C*H*=), 6.50 (dd, J = 7.9 Hz, 1.1 Hz, 1H, Ar), 7.10 (dt, J = 7.9 Hz, 1.6 Hz, 1H, Ar), 7.27 (d, J = 8.1 Hz, 2H, Ar), 7.34 (dt, J = 7.7 Hz, 1.1 Hz, 1H, Ar), 7.47-7.57 (m, 2H, Ar), 7.56-7.72 (m, 1H, Ar). FAB MS (relative intensity): 468 (M^++Na, 100), 446 (15), 388 (67), 314 (14), 176 (45). HRMS EI [M^+], Calcd.: 468.20045. Actual: 468.19871.



2-(*N,N*-homoallyltosylamino)benzyl alcohol (60). 2-(*N,N*-homoallyltosylamino)-benzyl-*tert*-butyldimethylsilyl ether (1.9 g, 4.2 mmol) was stirred with tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran, 13 mmol, 3 eq) at room temperature for 1 h. Once TLC showed the reaction was complete, the reaction medium was diluted with water (30 mL) and extracted with ether (3 x 30 mL). The combined organic extracts were then washed with brine (30 mL) and water (30 mL). They were dried over magnesium sulfate and concentrated *in vacuo*. The solvent was removed *in vacuo* to afford the title compound without further purification as a colourless oil (1.33 g, 4.0 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91-2.26 (m, 2H, NCH_2CH_2), 2.45 (s, 3H, ArMe), 2.95-3.26 (m, 1H, NCH_2), 3.87-4.05 (m, 1H, NCH_2), 4.42-4.56 (m, 1H, $ArCH_2O$), 4.93-5.08 (m, 3H, two $=CH_2$, one $ArCH_2O$), 5.54-5.77 (m, 1H, C*H*=), 6.31-6.51 (m, 1H, Ar), 7.09-7.19 (m, 1H, Ar), 7.27-7.32 (m, 2H, Ar), 7.31-7.40 (m, 1H, Ar), 7.46-7.55 (m, 2H, Ar), 7.53-7.68 (m, 1H, Ar).



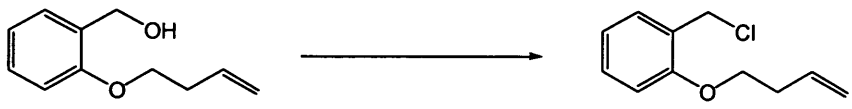
2-(*N,N*-homoallyltosylamino)benzyl chloride (61). 2-(*N,N*-homoallyltosylamino)benzyl alcohol (1.4 g, 4.2 mmol), was dissolved in dichloromethane (20 mL) with triethylamine (0.6 mL, 5.0 mmol, 1.0 eq). Thionyl chloride (0.35 mL, 4.62 mmol, 1.1 eq) was added dropwise at 0 °C, followed by stirring for 5 h at room temperature. The reaction mixture was diluted with dichloromethane (50 mL) and quenched with water (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of dichloromethane to afford the title compound as a light yellow solid (mp: 62 °C, 1.3 g, 3.7 mmol, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05-2.39 (m, 2H, NCH_2CH_2), 2.44 (s, 3H, ArMe), 2.98-3.30 (m, 1H, NCH_2), 3.73-4.03 (m, 1H, NCH_2), 4.64 (d, J = 12.4 Hz, 1H, $ArCH_2Cl$), 4.99-5.12 (m, 3H, two $=CH_2$, one $ArCH_2Cl$), 5.54-5.82 (m, 1H, $CH=$), 6.47-6.56 (m, 1H, Ar), 7.12-7.22 (m, 1H, Ar), 7.25-7.30 (m, 2H, Ar), 7.32-7.40 (m, 1H, Ar), 7.44-7.53 (m, 2H, Ar), 7.66 (dd, J = 7.8 Hz, 1.5 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 37.7, 42.0, 51.2, 117.3, 127.2, 128.1, 128.6, 128.9, 129.5, 131.1, 134.4, 134.6, 137.2, 139.7, 143.9. C.I. MS (relative intensity): 352 (^{37}Cl, M^+, 1) 350 (^{35}Cl, M^+, 4), 314 (14), 310 (24), 308 (78), 160 (16), 159 (100), 118 (40). HRMS C.I. [M^++H], Calcd.: 350.09815. Actual: 350.09870. IR (KBr, cm^{-1}): 3068, 2977, 2925, 1641, 1596, 1492, 1452, 1348, 1305, 1288, 1265, 1184, 1164, 1107, 1089, 1068, 1045, 991, 914, 891, 813, 763, 709, 684, 655, 580, 549.



(*N*-Tosyl)-4-methylene-2,3,4,5-tetrahydrobenzazepine (69). An oven-dried microwave vial was charged with 2-(*N,N*-homoallyltosylamino)benzyl chloride (70 mg, 0.20 mmol), dichlorobis(triphenylphosphine)palladium(II) (14 mg, 0.02 mmol, 0.10 eq), *N,N*-dicyclohexylmethylamine (86 μL, 0.40 mmol, 2.0 eq) and acetonitrile (1.5 mL). It was heated in a microwave reactor at 90 °C for 20 min. The crude residue was diluted with dichloromethane (5 mL) and immediately placed onto a column for silica gel chromatography in dichloromethane/petroleum ether (1:1) to afford the desired product as an off-white solid (61 mg, 98%, mp: 80 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H, ArCH_3), 2.47 (dd, J = 11.5 Hz, 5.9 Hz, 2H, NCH_2CH_2), 3.04 (s, 2H, ArCH_2C), 3.74 (br s, 2H, NCH_2), 4.70 (s, 1H, =C*H*), 4.78 (s,1H, =C*H*), 7.10-7.29 (m, 6H, Ar), 7.63 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 38.0, 42.3, 50.6, 112.7, 127.1, 127.2, 128.1, 128.4, 129.4, 129.5, 129.7, 138.8, 139.1, 139.4, 143.3, 143.8. E.I. MS (relative intensity): 313 (M^+, 35), 159 (9), 158 (M^+-Ts group, 100), 157 (12), 143 (10), 118 (12), 91 (14). HRMS E.I. [M^+], Calcd: 313.11365. Actual: 313.11294. IR (KBr, cm^{-1}): 2939, 2871, 1649, 1598, 1488, 1450, 1342, 1303, 1290, 1232, 1184, 1159, 1093, 1039, 916, 815, 779, 763, 732, 709, 690, 555, 536.

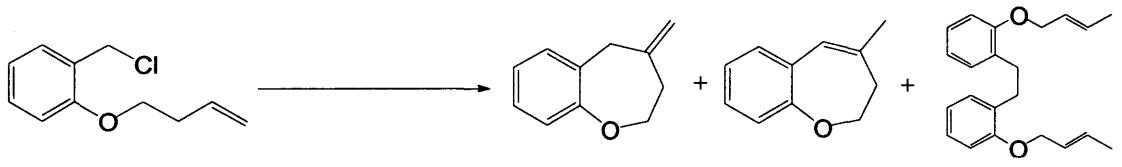
3.1.4. Preparation of 4-Methylene-2,3,4,5-tetrahydrobenzooxepine (70a).

2-Homoallyloxybenzyl alcohol (63). A solution containing saligenin (3.7 g, 30 mmol) and homoallyl bromide (4.6 mL, 30 mmol) in acetone (60 mL) was heated under reflux for 6 h in the presence of potassium carbonate (4.1 g, 30 mmol) and sodium iodide (1.1 g, 7.5 mmol). The reaction medium was diluted with water, extracted with diethyl ether (3 x 150 mL) and dried over magnesium sulfate. The solvent was then removed *in vacuo*. Flash column chromatography (silica gel) using an eluent of ethyl acetate/petroleum ether (3:7) gave the title compound as a colourless liquid (4.06 g, 22.8 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (q, *J* = 6.4 Hz, 2H, OCH_2CH_2), 3.92-4.15 (m, 2H, OCH_2CH_2), 4.67 (s, 2H, $ArCH_2OH$), 5.11-5.27 (m, 2H, $=CH_2$), 5.81-5.99 (m, 1H, $CH=CH_2$), 6.79-7.02 (m, 2H, Ar), 7.13-7.33 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8, 62.5, 66.8, 111.0, 117.5, 120.7, 128.8, 128.9, 129.3, 134.7, 156.9. E.I. MS (relative intensity): 178 (M^+, 96), 161 (50), 149 (18), 145 (13), 133 (37), 122 (31), 121 (33), 119 (24), 107 (51), 106 (100), 86 (34). HRMS EI [M^+], Calcd.:178.09883 . Actual: 178.09862. IR (KBr, cm^{-1}): 3417, 2933, 1737, 1373, 1242, 1157, 1047, 738.



2-Homoallyloxybenzyl chloride (64). 2-homoallyloxybenzyl alcohol (1.01 g, 5.6 mmol), was dissolved in dichloromethane (25 mL) with triethylamine (0.8 mL, 5.7 mmol, 1.0 eq). Thionyl chloride (0.46 mL, 6.27 mmol, 1.1 eq) was added dropwise at 0 °C, followed by stirring for 4 h at room temperature. The reaction mixture was

diluted with dichloromethane (50 mL) and quenched with water (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/petroleum ether (1:9) to give the title compound as a colourless liquid (0.95 g, 4.84 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (tq, *J* = 6.6 Hz, 1.2 Hz, 2H, OCH_2CH_2), 4.09 (t, *J* = 6.6 Hz, 2H, OCH_2CH_2), 4.68 (s, 2H, $ArCH_2OH$), 5.09-5.26 (m, 2H, $=CH_2$), 5.79-6.06 (m, 1H, $CH=CH_2$), 6.67-7.05 (m, 2H, Ar), 7.20-7.41 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.7, 41.6, 67.5, 111.8, 117.2, 120.7, 126.1, 130.0, 130.5, 134.5, 156.7. E.I. MS (relative intensity): 198 (^{37}C, M^+, 26), 196 (^{35}Cl, M^+, 96), 161 (22), 142 (31), 107 (100), 106 (72). HRMS EI [M^+], Calcd.: 196.06494. Actual: 196.06490. IR (KBr, cm^{-1}): 3078, 3043, 2968, 2929, 2873, 1643, 1602, 1589, 1494, 1471, 1438, 1319, 1294, 1249, 1218, 1107, 1047, 1031, 989, 914, 752, 671.

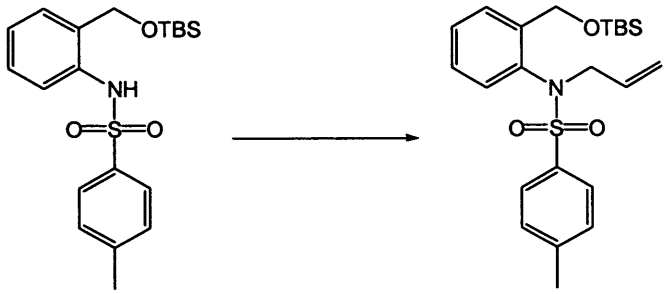


4-Methylene-2,3,4,5-tetrahydrobenzooxepine (70a)/ 4-Methyl-2,3-dihydrobenzooxepine (70b). An oven-dried microwave vial was charged with 2-homoallyloxybenzyl chloride (55 mg, 0.28 mmol), dichlorobis(triphenylphosphine)-palladium(II) (10 mg, 0.01 mmol, 0.05 eq), *N,N*-dicyclohexylmethylamine (120 μL, 0.56 mmol, 2.0 eq) and acetonitrile (1.5 mL). It was heated in a microwave reactor at 140 °C for 20 min. The crude residue was diluted with dichloromethane (20 mL) and quenched with water (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried

over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using ethyl acetate/petroleum ether (1:19). This afforded the products of the Heck reaction as a colourless oil (15 mg, 0.09 mmol, 33%). This was a 1:1 mixture of regioisomers where the olefin moiety was either exo- or endocyclic. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H, *endo* isomer, Me), 2.60 (t, 2H, J = 5.4 Hz, *endo* isomer, OCH_2CH_2), 2.65 (t, 2H, J = 5.5 Hz, *exo* isomer, OCH_2CH_2), 3.49 (s, 2H, *exo* isomer, $ArCH_2C$), 4.08 (t, 2H, J = 5.5 Hz, *exo* isomer, OCH_2), 4.22 (t, 2H, J = 5.4 Hz, *endo* isomer, OCH_2), 4.78 (s, 1H, *exo* isomer, $=CH_2$), 4.89 (s, 1H, *exo* isomer, $=CH_2$), 6.15 (s, 1H, *endo* isomer, ArCH=), 6.93-7.16 (m, 4H, *exo* isomer, Ar), 6.93-7.16 (m, *endo* isomer, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5 (*endo*), 38.7 (*endo*), 40.3 (*exo*), 42.3 (*exo*), 68.9 (*endo*), 72.6 (*exo*), 112.2 (*exo*), 114.1 (*exo*), 119.7 (*endo*), 121.2 (*exo*), 122.3 (*endo*), 123.7 (*exo*), 124.9 (*endo*), 126.7 (*endo*), 127.0 (*endo*), 127.6 (*exo*), 129.6 (*exo*), 132.2 (*endo*), 138.7 (*endo*), 144.7 (*exo*), 158.7 (*endo*), 159.8 (*exo*). C.I. MS (relative intensity): 175 (45), 161 (M^++H, 100), 147 (10), 133 (17), 121 (25), 107 (24), 91 (8). HRMS C.I. [M^+], Calcd.: 161.09663. Actual: 161.09685. IR (KBr, cm^{-1}): 2966, 2858, 1556, 1490, 1452, 1377, 1288, 1240, 1188, 1161, 1093, 1047, 1008, 964, 748. This reaction also afforded a rearrangement product as a colourless oil (12 mg, 13%). **(2-crotyloxy)phenethyl-(2-crotyloxybenzene) (71)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72-1.79 (m, 6H, $=CHCH_3$), 2.92 (d, J = 2.4 Hz, 4H, $ArCH_2$), 4.44-4.50 (m, 4H, OCH_2), 5.62-5.93 (m, 4H, CH=CH), 6.78-6.91 (m, 4H, Ar), 7.08-7.17 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 30.6, 68.7, 111.7, 120.3, 126.7, 126.8, 129.1, 129.9, 156.7. E.I. MS (relative intensity): 322 (M^+, 22), 268 (17), 180 (14), 161 (48), 137 (50), 107 (100), 83 (63). HRMS EI [M^+], Calcd.: 322.19273. Actual: 322.19255.

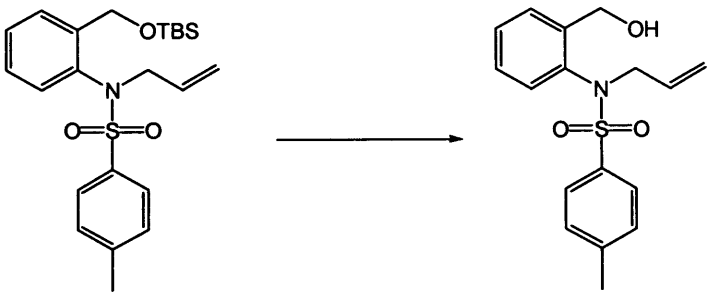
IR (KBr, cm^{-1}): 2927, 1560, 1544, 1501, 1490, 1548, 1438, 1263, 1228, 1110, 1047, 1018, 995, 752, 727.

3.1.5. Preparation of N,N-allyl(2-chloromethylphenyl)p-toluenesulfonamide (68)

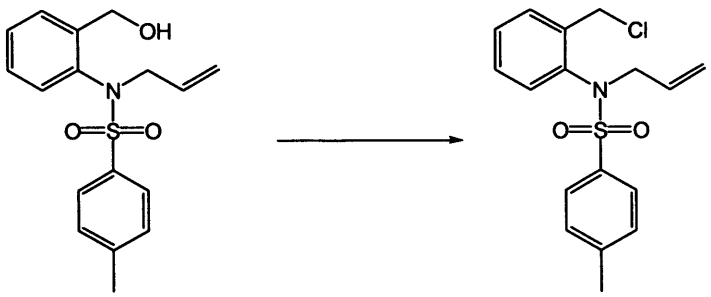


2-(*N,N*-allyltosylamino)benzyl-*tert*-butyldimethylsilyl ether (66). A solution containing 2-(*N*-tosylamino)benzyl-*tert*-butyldimethylsilyl ether (4.2 g, 13.25 mmol) and allyl bromide (1.1 mL, 13.25 mmol) in acetone (60 mL) was heated under reflux overnight in the presence of potassium carbonate (1.8 g, 13.25 mmol). The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with water (200 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* affording the title compound as a white solid (mp: 107 °C. 4.39 g, 10.2 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 6H, SiMe), 0.96 (s, 1H, Si-^{t}Bu), 2.45 (s, 3H, SO_2PhCH_3), 3.69-3.89 (m, 1H, NCH_2), 4.29-4.45 (m, 1H, NCH_2), 4.81-5.05 (m, 4H, $ArCH_2O$, $=CH_2$), 5.64-5.82 (m, 1H, C*H*=), 6.49 (d, *J* = 7.9 Hz, 1H, Ar), 7.08 (dt, *J* = 7.6 Hz, 0.9 Hz, 1H, Ar), 7.25-7.36 (m, 3H, Ar), 7.55 (d, *J* = 8.2 Hz, 2H, Ar), 7.59-7.65 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, 18.4, 21.6, 26.0, 54.9, 61.4, 119.6, 126.8, 127.5, 127.6, 128.1, 128.5, 129.5, 132.3, 135.5, 135.9, 143.2, 143.6. FAB MS (relative intensity): 549 (3), 470 (2), 454 (M^++Na, 100), 430 (8), 374 (50), 301 (17), 277 (5), 237 (3), 219 (19). HRMS FAB [M^++Na], Calcd.: 454.18480. Actual: 454.18311. IR

(KBr, cm^{-1}): 2927, 2856, 1510, 1492, 1460, 1352, 1255, 1222, 1164, 1120, 1082, 1004, 927, 839, 8132, 777, 713, 665, 576, 549.

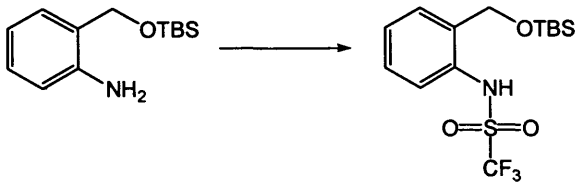


2-(*N,N*-allyltosylamino)benzyl alcohol (67). 2-(*N,N*-allyltosylamino)benzyl-*tert*-butyl-dimethylsilyl ether (4.2 g, 9.75 mmol) was stirred with tetra-*n*-butylammonium fluoride (1 M in THF, 39 mmol, 4.0 eq) at room temperature for 1 h. Once TLC showed that the reaction was complete, the reaction mixture was diluted with water (70 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were washed with brine (70 mL) and water (70 mL). They were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/petroleum ether (3:7) affording the title compound as a white solid (mp: 62 °C, 2.95 g, 9.3 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H, SO_2PhCH_3), 2.85 (br s, 1H, O*H*), 3.72 (dd, *J* = 13.3 Hz, 8.3 Hz, 1H, NCH_2), 4.51 (d, *J* = 11.8 Hz, 1H, $ArCH_2O$), 4.88-5.05 (m, 2H, $=CH_2$), 5.67-5.81 (m, 1H, C*H*=), 6.43 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H, Ar), 7.13 (dt, *J* = 7.7 Hz, 1.6 Hz, 1H, Ar), 7.23-7.39 (m, 3H, Ar), 7.49-7.62 (m, 3H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 55.1, 61.2, 120.0, 127.5, 127.5, 128.1, 128.3, 129.1, 129.6, 131.1, 131.9, 142.4, 144.0. CI+ MS (relative intensity): 461 (22), 318 (M^++H, 24), 300 (100), 253 (2), 236 (12), 162 (68), 144 (80), 123 (1), 92 (2). HRMS CI [M^++H], Calcd.: 318.11638. Actual: 318.11580. IR (KBr, cm^{-1}): 3415, 3028, 2877, 1492, 1454, 1388, 1261, 1226, 1193, 1143, 1047, 970, 898, 800.

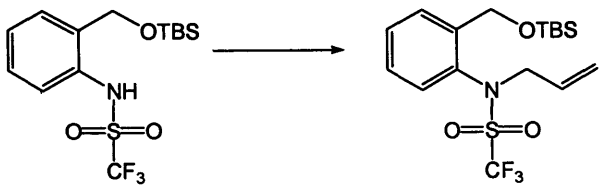


2-(*N,N*-allyltosylamino)benzyl chloride (68). 2-(*N,N*-allyltosylamino)benzyl alcohol (1.6 g, 5.0 mmol), was dissolved in dichloromethane (25 mL) with triethylamine (0.7 mL, 5.0 mmol, 1.0 eq). Thionyl chloride (0.4 mL, 5.50 mmol, 1.1 eq) was added dropwise at 0 °C, followed by stirring for 5 h at room temperature. The reaction mixture was diluted with dichloromethane (50 mL) and quenched with water (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the chloride as a light yellow solid (1.27 g, 4.9 mmol, 98%, mp: 66 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, SO_2PhCH_3), 3.72-3.95 (m, 1H, NCH_2), 4.53 (dd, J = 52.8 Hz, 11.5 Hz, 2H, one NCH_2, one $ArCH_2O$), 4.95-5.07 (m, 3H, one $ArCH_2O$, two $=CH_2$), 5.62-5.88 (m, 1H, $CH=$), 6.49-6.57 (m, 1H, Ar), 7.15 (dt, J = 7.7 Hz, 1.3 Hz, 1H, Ar), 7.23-7.38 (m, 3H, Ar), 7.52 (d, J = 8.2 Hz, 2H, Ar), 7.61 (dd, J = 7.8 Hz, 1.0 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 21.5, 25.8, 65.1, 122.3, 124.5, 127.0, 128.0, 128.8, 129.6, 130.6, 137.0. CI+ MS (relative intensity): 336 (M^++H, 14), 300 (100), 236 (20), 180 (45), 146 (48), 145 (90), 144 (87), 139 (7), 118 (6). HRMS CI [M^++H], Calcd.: 336.08250. Actual: 336.08157. IR (KBr, cm^{-1}): 3084, 3031, 2927, 2860, 1643, 1598, 1492, 1452, 1348, 1305, 1290, 1184, 1164, 1091, 1058, 927, 864, 813, 767, 707, 665, 640, 586, 570, 547.

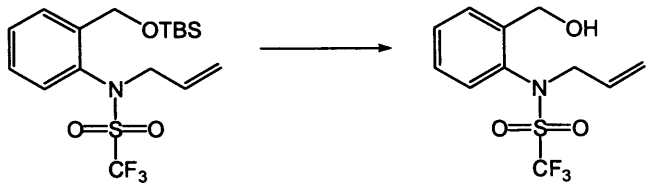
3.1.6. Preparation and N-allyl(2-chloromethyl-phenyl)trifluoromethanesulfonamide (75) and 2-(N-triflicamino)benzyltriethylammonium chloride (76).



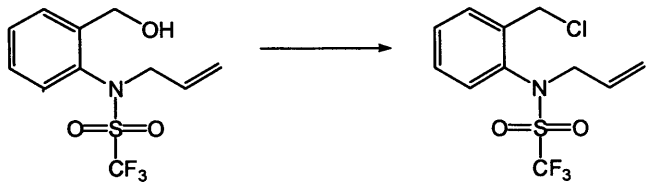
2-(*N*-Triflicamino)benzyl-*tert*-butyldimethylsilyl ether (72). 2-Aminobenzyl-*tert*-butyldimethylsilyl ether (5.9 g, 25 mmol) was dissolved in dry dichloromethane (150 mL) with sodium carbonate (2.6 g, 25 mmol, 1.0 eq) in a 3-necked flask under nitrogen at -78 °C. Triflic anhydride (4.2 mL, 25 mmol, 1.0 eq) in dichloromethane (50 mL) was added dropwise to the reaction medium. The mixture was allowed to warm to room temperature and was stirred for an additional 2 h, after which it was diluted with water (150 mL). It was extracted with dichloromethane (2 x 250 mL), and the combined organic phases were dried over magnesium sulfate. The organic extracts were concentrated *in vacuo* to afford the title compound as a light yellow solid without further purification (4.3 g, 11.7 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H, SiMe), 0.92 (s, 9H, *t*-Bu), 4.82 (s, 2H, CH_2), 7.14 (m, 2H, Ar), 7.32 (dt, J = 3.8 Hz, 2.0 Hz, 1H, Ar), 7.57 (d, J = 7.5 Hz, 1H, Ar), 9.19 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.61, -3.62, 18.0, 25.6, 65.6, 121.7, 125.9, 128.1, 129.2, 130.3, 135.4. C.I. MS (relative intensity): 370 (M^++H, 4), 312 (37), 266 (23), 238 (100), 179 (28). HRMS C.I. [M^++H], Calcd.: 370.11199. Actual: 370.11038. IR (KBr, cm^{-1}): 2954, 2931, 2885, 2858, 1496, 1471, 1423, 1384, 1361, 1257, 1226, 1197, 1145, 1107, 1056, 1004, 956, 837, 813, 759, 605.



2-(*N,N*-Allyltriflicamino)benzyl-*tert*-butyldimethylsilyl ether (73). 2-(*N*-triflicamino)-benzyl-*tert*-butyldimethylsilyl ether (3.7 g, 10 mmol) was dissolved in acetone (250 mL) with potassium carbonate (1.38 g, 10 mmol, 1.0 eq) and allyl bromide (0.87 mL, 10 mmol, 1.0 eq) and heated under reflux overnight. When the reaction was shown to be complete, the reaction mixture was diluted with water (200 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with brine (200 mL) and water (200 mL) and were dried over magnesium sulfate. The solvent was removed *in vacuo* to give the product as a yellow oil without further purification (3.45 g, 8.4 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H, SiMe), 0.92 (s, 9H, *t*-Bu), 4.28 (d, J = 6.9 Hz, 2H), 4.80 (d, J = 4.1 Hz, 2H), 5.06 (dq, J = 16.8 Hz, 1.2 Hz, 1H), 5.13 (d, J = 1.0 Hz, 1H), 5.79 (m, 1H, CH=), 7.14 (d, J = 8.3 Hz, 1H, Ar), 7.26 (dt, J = 7.4 Hz, 1.7 Hz, 2H, Ar), 7.38 (dt, J = 7.4 Hz, 1.2Hz, 1H, Ar), 7.59 (d, J = 7.8 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.6, -3.5, 18.4, 25.7, 56.6, 61.2, 121.6, 127.8, 128.8, 129.3, 129.8, 130.8, 134.2, 141.9. C.I. MS (relative intensity): 410 (M^++H, 8), 394 (27), 352 (54), 278 (67), 238 (17), 144 (100), 115 (22). HRMS CI [M^++H], Calcd.: 410.14329. Actual: 410.14250. IR (KBr, cm^{-1}): 3442, 2954, 2929, 1392, 1226, 1193, 1143, 1122, 839, 779, 748



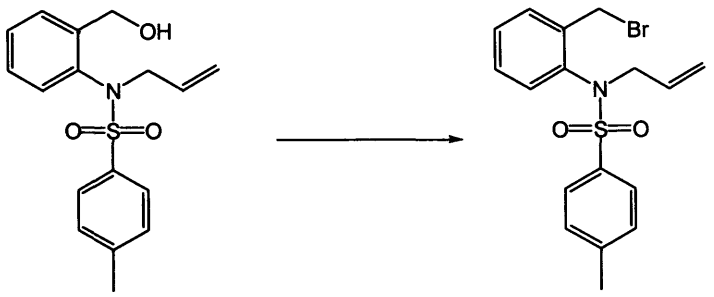
2-(*N,N*-Allyltriflicamino)benzyl alcohol (74). 2-(*N,N*-allyltriflicamino)benzyl-*tert*-butyldimethylsilyl ether (3.45 g, 8.4 mmol) was stirred with tetra-*n*-butylammonium fluoride (1 M in THF, 25.2 mmol, 3.0 eq) at room temperature for 1 h. Once TLC showed the reaction to be complete, the mixture was diluted with water (70 mL) and extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were washed with brine (70 mL) and water (70 mL). They were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/*iso*-hexane (1:19 to 2:3) to afford the title compound as a yellow oil (1.95 g, 6.6 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05-2.30 (br, 1H, OH), 4.25 (m, 1H, NCH_2), 4.43 (m, 1H, NCH_2), 4.71 (dd, J = 11.1 Hz, 44.4 Hz, 2H, ArCH_2OH). 5.07 (d, J = 18.1 Hz, 1H, =CH_2), 5.18 (d, J = 11.1 Hz, 2H, =CH_2), 5.74-5.87 (m, 1H, CH=), 7.24 (d, J = 8.3 Hz, 1H, Ar), 7.36 (t, J = 8.3 Hz, 1H, Ar), 7.44 (t, J = 8.3 Hz, 1H, Ar), 7.63 (d, J = 8.3 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 60.9, 122.0, 129.0, 129.2, 130.2, 130.7, 134.6, 141.2. FAB MS (relative intensity): 318 (M^++Na, 100), 279 (5), 200 (8), 177 (20). HRMS FAB. [M^++Na], Calcd.: 318.03877. Actual: 318.03821. IR (KBr, cm^{-1}): 3417, 1643, 1556, 1492, 1454, 1421, 1388, 1311, 1284, 1226, 1190, 1155, 1110, 1045, 995, 933, 877, 798, 769, 711, 655, 609, 574, 528.



2-(*N,N*-Allyltriflicamino)benzyl chloride (75). 2-(*N,N*-Allyltriflicamino)benzyl alcohol (1.2 g, 4.0 mmol) was dissolved in dichloromethane (60 mL) with triethylamine (558 μL, 4.0 mmol, 1.0 eq). Thionyl chloride (321 μL, 4.0 mmol, 1.1 eq) was added dropwise at 0 °C, followed by stirring for 5 h at room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to give the title compound as a yellow oil (1.24 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, J = 7.3 Hz, 2H), 4.62 (d, J = 12.3 Hz, 1H), 4.80 (d, J = 12.3 Hz, 1H), 5.12 (dq, J = 1.2 Hz, 17.0 Hz, 1H), 5.22 (dd, J = 1.0 Hz, 10.0 Hz, 1H), δ 5.87 (m, 1H, CH=), 7.23 (d, J = 8.3 Hz, 2H, Ar), 7.38 (dt, J = 1.8 Hz, 4.0 Hz, 1H), 7.46 (dt, J = 1.3 Hz, 3.8 Hz, 1H, Ar), 7.64 (dd, J = 1.6 Hz, 7.6 Hz, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.4, 56.7, 122.2, 129.4, 130.0, 130.3, 130.6, 131.6, 134.8, 138.1. E.I. MS (relative intensity): 237 (30), 180 (35), 144 (100), 130 (25), 118 (30), 117 (35), 91 (45), 89 (15), 69 (15). HRMS E.I. [M^+], Calcd.: 313.01456. Actual: 313.01410. IR (KBr, cm^{-1}): 3085, 3033, 2985, 2937, 1492, 1454, 1421, 1392, 1353, 1311, 1286, 1267, 1226, 1193, 1155, 1132, 1101, 1056, 993, 955, 879, 813, 769, 725, 682, 655, 609, 528, 489.

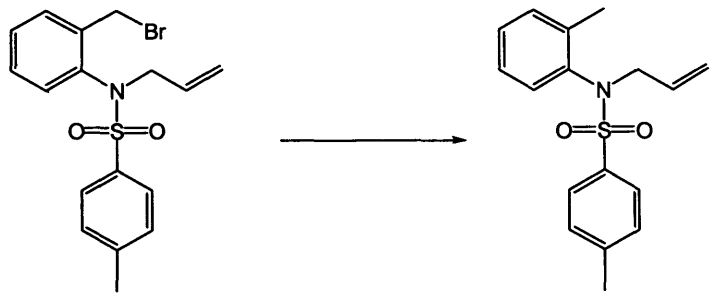
2-(*N*-Triflicamino)benzyltriethylammonium chloride (76). An oven-dried Schlenk tube was charged with 2-(*N,N*-allyltriflicamino)benzyl chloride (408 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (75 mg, 0.08 mmol, 0.05 eq). It was sealed with a septum and cycled with N_2/vacuum three times. Triethylamine (362 μL, 3.0 mmol, 2.0 eq) and acetonitrile (25 mL) were added *via* syringe and the mixture was stirred at room temperature for 3 h until TLC showed that the benzyl chloride was fully consumed. The mixture was diluted with ethyl acetate (50 mL) and quenched with water (100 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The product was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:9) to afford the title compound as a white solid (decomposes at 155 °C, 80 mg, 0.21 mmol, 16%). ^{1}H NMR (300 MHz, CD_3CN): δ 1.30 (t, J = 7.2 Hz, 9H, CH_2CH_3), 3.22 (q, J = 7.2 Hz, 6H, CH_2CH_3), 4.38 (s, 2H, $ArCH_2$), 6.81-6.87 (m, 1H, Ar), 7.21-7.28 (m, 2H, Ar), 7.49-7.60 (m, 1H, Ar). ^{13}C NMR (75 MHz, CD_3CN): δ 8.64, 53.8, 58.4, 120.6, 121.4, 123.8, 131.7, 133.9, 142.7, 150.8. E.S.I. MS (relative intensity): 339 (M^+, 100), 292 (15), 260 (36), 238 (14), 182 (12). HRMS E.S.I. [M^+], Calcd.: 339.13541. Actual: 339.13564. IR (KBr, cm^{-1}): 2927, 2856, 1596, 1571, 1510, 1483, 1450, 1382, 1303, 1272, 1199, 1155, 1091, 1047, 995.

3.1.7. Preparation of (N-Tosyl)-3-methylene-2,3,4-tetrahydroquinoline (82).

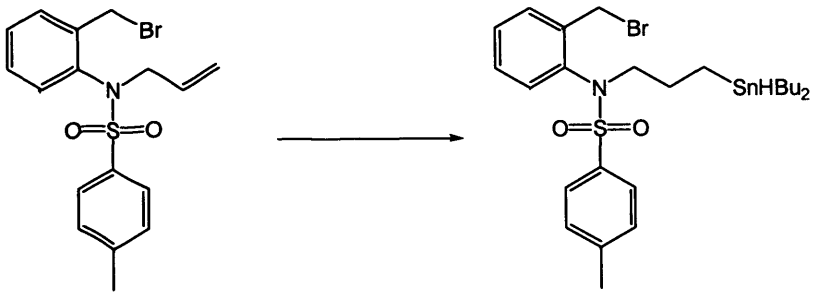


2-(*N,N*-Allyltosylamino)benzyl bromide (77). 2-(*N,N*-allyltosylamino)benzyl alcohol (0.95 g, 3.0 mmol), *N*-bromosuccinimide (0.80 g, 4.5 mmol, 1.5 eq), potassium hydroxide (337 mg, 6.0 mmol, 2.0 eq) and triphenylphosphine (1.2 g, 4.5 mmol, 1.5 eq) were dissolved in chloroform (30 mL) and stirred overnight at room temperature. The mixture was diluted with dichloromethane (50 mL) and extracted with water (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) twice using an eluent of ethyl acetate/hexane (1:19) to ensure removal of the triphenylphosphine. This afforded the title compound as a colourless oil (546 mg, 1.44 mmol, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, SO_2PhCH_3), 3.72-4.02 (m, 1H, NCH_2), 4.34-4.54 (m, 2H, one NCH_2, one $ArCH_2O$), 4.89-5.10 (m, 3H, one $ArCH_2O$, two $=CH_2$), 5.72-5.92 (m, 1H, C*H*=), 6.50-6.55 (m, 1H, Ar), 7.13 (dt, J = 7.7 Hz, 1.6 Hz, 1H, Ar), 7.22-7.36 (m, 3H, Ar), 7.49-7.54 (m, 2H, Ar), 7.59 (dd, J = 7.7 Hz, 1.6 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 29.4, 54.6, 119.8, 128.1, 128.3, 128.6, 129.0, 129.6, 132.0, 132.4, 137.2, 139.5, 143.9. E.I. MS (relative intensity): 381 (M^+,18), 379 (M^+, 20), 354 (15), 353 (22), 352 (20), 300 (100), 226 (83), 224 (85), 194 (43), 180 (33), 155 (58), 145 (83), 144 (92), 143 (43), 130 (67), 118 (75), 117 (59), 116 (38), 115 (27), 104 (15), 92 (53), 91 (68), 90 (58). HRMS EI [M^+], Calcd.: 379.02361.

Actual: 379.02214. IR (KBr, cm^{-1}): 3064, 3028, 2923, 1596, 1492, 1452, 1348, 1164, 1091, 1056, 813, 663, 586, 569, 547.

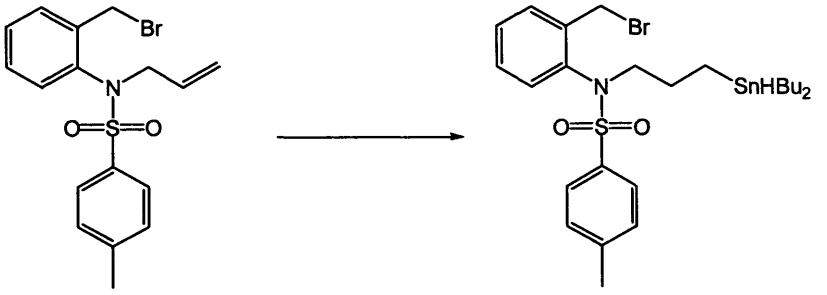


2-(*N,N*-Allyltosylamino)toluene (78). 2-(*N,N*-allyltosylamino)benzyl bromide (103 mg, 0.27 mmol) was dissolved in benzene (8 mL). Tributyltin hydride (145 μL, 0.54 mmol, 1.5 eq) and azobisisobutylonitrile (3 mg, 0.02 mmol, 0.06 eq) in benzene (2 mL) were added next and the mixture was heated under reflux for 6 h. It was allowed to cool to room temperature and was filtered through celite. The filtrate was concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (1:9 potassium carbonate/silica gel) using an eluent of ethyl acetate/petroleum ether (1:19) affording the title compound as a colourless oil (21 mg, 0.06 mmol, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, ArCH_3), 2.45 (s, 3H, SO_2PhCH_3), 3.86-3.89 (m, 1H, NCH_2), 4.32-4.35 (m, 1H, NCH_2), 4.94-5.01 (m, 2H, =CH_2), 5.70-5.79 (m, 1H, CH=), 6.56-6.58 (m, 1H, Ar), 7.02-7.29 (m, 5H, Ar), 7.48-7.99 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 21.6, 35.5, 54.7, 119.2, 126.1, 128.0, 128.3, 128.4, 129.1, 129.5, 129.6, 131.3, 132.5, 136.2, 138.0, 140.1, 143.4. E.I. MS (relative intensity): 301 (M^+, 8), 237 (4), 196 (5), 146 (45), 130 (40), 118 (51), 91 (100). HRMS E.I. [M^+], Calcd.: 301.11364. Actual: 301.11371. IR (KBr, cm^{-1}): 2958, 2925, 1598, 1492, 1454, 1348, 1305, 1164, 1120, 1091, 1066, 1041, 871, 815, 804, 731, 713, 663, 582, 543. The starting material 2-(*N,N*-allyltosylamino)benzyl bromide (**25**) was also recovered (48 mg, 0.16 mmol, 59%).

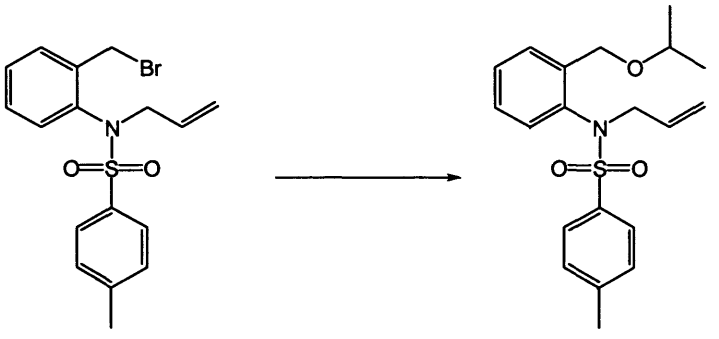


***N,N*-(2-Bromomethylphenyl)-(3-dibutylstannanylpropyl)-*p*-toluenesulfonamide (79).** 2-(*N,N*-allyltosylamino)benzyl bromide (95 mg, 0.25 mmol) was dissolved in benzene (8 mL). Tributyltin hydride (67 μL, 0.25 mmol, 1.0 eq) and azobisisobutylonitrile (2.0 mg, 0.02 mmol, 0.06 eq) in benzene (2 mL) were added and the mixture was heated under reflux at 90 °C for 16 h. The reaction was allowed to cool to room temperature and diluted with ether (20 mL). It was filtered through celite, after which the filtrate was concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (1:9 potassium carbonate/silica gel) with an eluent of ethyl acetate/petroleum ether (1:19) affording the title compound as a colourless oil (50 mg, 0.08 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79-0.89 (m, 6H, Sn*Bu*), 1.10-1.45 (m, 12H, Sn(CH_2)$_3$), 1.45-1.63 (m, 2H, N(CH_2)$_2$$CH_2$Sn), 1.72-1.87 (m, 2H, NCH$_2$$CH_2$), 2.44 (s, 3H, Ar$CH_3$), 2.99-3.20 (m, 1H, N$CH_2$), 3.66-3.89 (m, 1H, N$CH_2$), 4.46-4.55 (m, 1H, CH_2Br), 4.98-5.08 (m, 1H, CH_2Br), 6.43-6.53 (m, 1H, Ar), 7.06-7.18 (m, 1H, Ar), 7.30 (dd, J = 16.6 Hz, 7.8 Hz, 3H, Ar), 7.42-7.54 (m, 2H, Ar), 7.54-7.68 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 5.5, 8.8, 13.7, 21.6, 26.4, 27.0, 27.4, 27.7, 29.2, 29.4, 55.7, 127.3, 128.1, 128.6, 128.7, 129.5, 132.1, 134.8, 137.6, 139.8, 143.7. E.S.I. MS (relative intensity): 616 (M^++H, 100), 615 (M^+, 98), 612 (45), 579 (17), 548 (18), 515 (16), 481 (22), 470 (15), 429 (35), 408 (47), 374 (64), 352 (22), 332 (67), 330 (35), 261 (25), 217 (43), 196 (18), 178 (40). HRMS E.S.I [M^+], Calcd.: 615.08286. Actual: 615.08474. IR (KBr, cm^{-1}): 2954, 2923, 2869, 2852, 1598, 1492, 1454, 1350, 1159, 1091, 1060, 1043, 1020, 904, 813, 761, 713,

692, 619, 582, 549, 507. The starting material 2-(*N,N*-allyltosylamino)benzyl bromide was also recovered (40 mg, 0.11 mmol, 42%).



***N,N*-(2-Bromomethylphenyl)-(3-dibutylstannanylpropyl)-*p*-toluenesulfonamide (79).** 2-(*N,N*-allyltosylamino)benzyl bromide (19 mg, 0.05 mmol) was dissolved in benzene (5 mL). Tributyltin hydride (13 μL, 0.05 mmol, 1.0 eq) and AIBN (0.0005mg, 0.003 mmol, 0.06 eq) in benzene (1 mL) were added dropwise at reflux at 90 °C over 7 h followed by reflux for a further 16 h. The reaction was allowed to cool to room temperature and diluted with ether (20 mL). It was filtered through celite and the filtrate was concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (1:9 potassium carbonate/silica gel) using an eluent of ethyl acetate/petroleum ether (1:19), to afforded the title compound as a colourless oil (11 mg, 0.02 mmol, 36%). Spectral data as above.



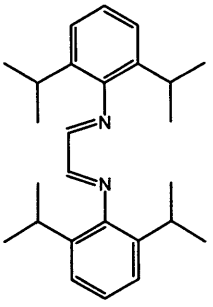
2-(*N,N*-Allyltosylamino)benzyl *iso*-propylether (81). Nickel iodide (9 mg, 0.03 mmol, 0.06 eq), *trans*-2-aminocyclohexanol hydrochloride (5 mg, 0.03 mmol, 0.06

eq), sodium hexamethyldisilazide (0.183 g, 2.0 mmol, 2.0 eq) and phenylboronic acid (73 mg, 1.2 mmol, 1.2 eq) were placed in a Schlenk tube. The flask was sealed and cycled with nitrogen/vacuum three times and 2-propanol (1 mL) was added slowly. After stirring for 5 min at room temperature, 2-(*N,N*-allyltosylamino)benzyl bromide (190 mg, 2.0 mmol, 1.0 eq) in 2-propanol (1 mL) was added, followed by stirring at 60 °C for 48 h. The mixture was then cooled to room temperature. It was diluted with dichloromethane (100 mL) and filtered through a short pad of silica. The solvent was removed *in vacuo* and the crude residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/hexane (1:9) to afford the title compound as a colourless oil (97 mg, 0.26 mmol, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6H, $CH(CH_3)_2$), 2.43 (s, 3H, SO_2PhCH_3), 3.61-3.76 (m, 1H), 3.76-3.97 (m, 1H), 4.19-4.47 (m, 1H), 4.55-4.81 (m, 1H), 4.94-4.99 (m, 1H), 4.99-5.04 (m, 1H), 5.63-5.85 (m, 1H), 6.52 (dd, J = 8.0 Hz, 0.8 Hz, 1H, Ar), 7.09 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 7.23-7.35 (m, 3H, Ar), 7.51-7.58 (m, 2H, Ar), 7.61 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.3, 54.9, 66.0, 71.5, 119.5, 127.3, 127.8, 128.0, 128.6, 129.0, 129.5, 132.3, 135.6, 136.8, 141.2, 143.6. FAB MS (relative intensity): 398 (3), 382 (M^++Na, 100), 360 (8), 301 (17), 220 (7), 176 (17). HRMS FAB [M^++Na], Calcd.: 382.14528. Actual: 382.14435. IR (KBr, cm^{-1}): 2972, 2927, 2869, 1596, 1492, 1452, 1350, 1305, 1288, 1222, 1164, 1124, 1091, 1062, 997, 925, 864, 813, 715, 665, 576, 551.

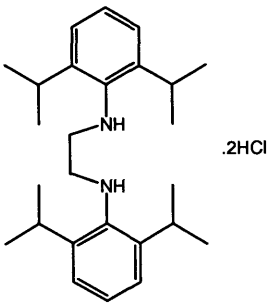
(*N*-Tosyl)-3-methylene-2,3,4-tetrahydroquinoline (82). Anhydrous cobalt(II) chloride (7 mg, 0.05 mmol) was placed in a Schlenk tube with 1,4-bis-(diphenylphosphino)butane (25 mg, 0.06 mmol). The tube was sealed with a septum and cycled with nitrogen/vacuum three times. Tetrahydrofuran (1 mL) was added *via* syringe and the mixture was stirred at room temperature for 10 min. This was followed by the addition of trimethylsilylmethylmagnesium chloride (1.0 M solution in ether, 1.5 mL, 1.5 mmol) at 0 °C, affording a dark blue solution. After 5 min, 2-(*N,N*-allyltosylamino)benzyl bromide (0.19 g in 1 mL of tetrahydrofuran, 0.50 mmol) was added *via* syringe. The mixture was placed in an oil bath at 80 °C for 10 min, at which time TLC showed the full consumption of the starting material. The mixture was poured into saturated ammonium chloride solution and was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (silica gel) using an eluent of ethyl acetate/petroleum ether (1:9) to afford the title compound as a colourless oil (17 mg, 0.06 mmol, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, ArCH_3), 2.44 (s, 2H, NCH_2), 2.88 (s, 2H, ArCH_2C), 4.72 (s, 1H, =C*H*), 4.87 (s, 1H, =C*H*), 7.10-7.37 (m, 6H, Ar), 7.72 (dd, J = 8.0 Hz, 1.1 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 33.4, 51.9, 110.9, 126.6, 126.7, 127.2, 127.3, 127.6, 128.3, 129.1, 129.6, 132.2, 136.9, 139.5, 143.4, 143.8. C.I. MS (relative intensity): 302 (20), 300 (M^++1, 18), 236 (15), 214 (14), 189 (32), 146 (95), 122 (40), 106 (100), 98 (65), 90 (89). HRMS C.I. [M^++H], Calcd.: 300.10582. Actual: 300.10634. IR (KBr, cm^{-1}): 2955, 2928, 1488, 1454, 1384, 1350, 1305, 1213, 1164, 1091, 1064, 1035, 813, 790, 763, 713, 663, 576, 543.

3.2. Synthesis of Imidazolium Salts and Palladium Catalysts

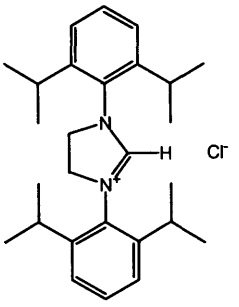
Preparation of SIPr.HCl



3.2.1. Glyoxal-bis-(2,6-diisopropylphenyl)imine.[36] 40 % aqueous glyoxal (18.15 g, 120 mmol glyoxal) was added to *n*-propanol (20 mL) and water (50 mL). This solution was added at ambient temperature to 2,6-diisopropylphenylamine (50.0 g, 280 mmol, 2.25 eq) in *n*-propanol (200 mL) and was heated at 70 °C for 1 h. Upon cooling to room temperature, water (200 mL) was added, causing the precipitation of the diimine. After filtration, the precipitate was dissolved in the minimum amount of hot *n*-propanol (75 mL), after which water (200 mL) added to effect re-precipitation. The solid was collected and dried under vacuum over P_2O_5 overnight to afford the title compound as a yellow solid (37.5 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (d, J = 6.9 Hz, 24H, $CH(CH_3)_2$), 2.9 (m, 4H, $CH(CH_3)_2$), 7.10-7.25 (m, 6H, Ar), 8.08 (s, 2H, imine CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 28.1, 123.2, 125.1, 136.7, 148.0, 163.1. EI MS (relative intensity): 377 (M^++H, 55), 333 (100), 228 (5), 200 (12), 146 (8). HRMS E.I. [M^++H], Calcd.: 377.29566. Actual: 377.29613. IR (KBr, nujol mull, cm^{-1}): 3063, 2963, 2871, 1626, 1443, 1360, 1331, 1261, 1175, 1103, 1051, 961, 924, 889, 795, 752, 706, 677.

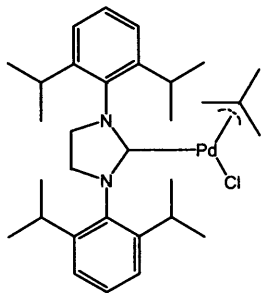


3.2.2. *N,N'*-Bis-(2,6-diisopropylphenylamine)ethane dihydrochloride.[36] Glyoxal-bis-(2,6-diisopropylphenyl)imine (10.0 g, 26.6 mmol) and sodium borohydride (4.2 g, 112 mmol, 4.2 eq) were placed in a two-necked flask fitted with a reflux condenser and a septum. The reaction set-up was cycled between vacuum and argon three times and left opened to the argon flow. Dry tetrahydrofuran (100 mL) was added and the solution was heated under reflux for 21 h under argon. Upon cooling to ambient temperature, 5M HCl (90 mL) was added dropwise until effervescence had stopped. The resulting precipitate was collected *via* filtration and washed with water (70 mL) and ether (2 x 70 mL). It was dried *in vacuo* to give 9.7 g (80%) of the title compound as a white solid. ^{1}H NMR (300 MHz, d_6-DMSO): δ 1.18 (d, J = 7.7 Hz, 24H, CH*Me*$_2$), 3.26-3.37 (m, 4H, C*H*Me$_2$), 3.7-4.8 (br s, 4H, NCH$_2$), 7.26 (s, 6H, Ar),. EI MS (relative intensity): 380 (M^+, 68), 190 (100), 160 (81), 132 (45), 91 (19), 43 (18). HRMS E.I. [M^+], Calcd.: 380.31913. Actual: 380.32040.



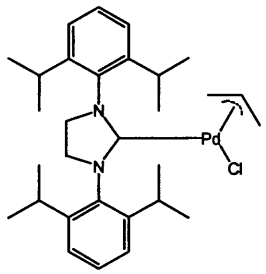
3.2.3. 1,3-Bis-(2,6-diisopropylphenyl)imidazolinium Chloride.[36] *N,N'*-Bis-(2,6-diisopropylphenylamine)ethane dihydrochloride (7.5 g, 16.5 mmol), triethyl orthoformate (90 mL) and 4 drops of formic acid were charged to a round bottomed flask with a magnetic stirrer. The flask was fitted with a reflux condenser and heated under reflux for 48 h whilst open to the air. The mixture was cooled to room temperature and the resulting precipitate was collected *via* filtration. The solid was heated *in vacuo* at 70 °C for 48 h to remove any excess triethyl orthoformate, affording the title compound as a white solid (4.4 g, 62%, mp: 242 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, J = 6.7 Hz, 12H, $CH(CH_3)_2$), 1.33 (d, J = 6.7 Hz, 12H, $CH(CH_3)_2$), 3.02-3.11 (m, 4H, $CH(CH_3)_2$), 4.52 (s, 4H, imid-CH_2), 7.40-7.57 (m, 6H, Ar), 9.46 (s, H, imid-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3, 24.9, 28.2, 53.6, 124.8, 129.8, 131.1, 146.1, 160.1. EI MS (relative intensity): 391 (M^+, 18), 390 (60), 389 (100), 375 (14), 347 (16), 241 (20), 188 (81), 172 (20), 146 (62), 91 (12). HRMS E.I. [M^++H], Calcd.: 391.31131. Actual: 391.31074. IR (KBr, cm^{-1}) 3049, 2964, 2926, 2874, 1628, 1456, 1393, 1369, 1263, 1192, 1059, 808, 729.

Preparation of isolated Pd-NHC complexes



3.2.4. (SIPr)Pd(methallyl)Cl. A two-necked flask with a magnetic stirrer was charged with SIPr.HCl (1.9 g, 4.2 mmol) and potassium *tert*-butoxide (0.4 g, 3.6 mmol). A septum was placed on one neck and the remaining neck was attached to a nitrogen line, after which the flask was cycled with nitrogen and vacuum three times. Under a positive flow of nitrogen, technical grade *iso*-propanol (35 mL) was added *via* syringe through the septum and the mixture was stirred for 2 h at 80 °C. After cooling to room temperature over 45 min, the septum was removed, $[Pd(methallyl)Cl]_2$ (0.55 g, 1.5 mmol) was added quickly and the septum was replaced. The mixture was stirred for 2 h at room temperature, over which time its colour gradually turned grey. It was opened to the air and stirred for 15 min. Water (100 mL) was added and a solid precipitated. The water was removed by filtration and the solid was taken up in chloroform (100 mL). This solution was filtered through phase separating filter paper to remove the water and was concentrated *in vacuo* giving a yellow oil. This crude residue was purified using flash column chromatography (silica gel) with an eluent of diethyl ether/petroleum spirit (3:2) to afford the desired complex as an off-white crystalline solid (1.02 g, 2.17 mmol, 72%, decomposes at 155 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_2CMeCH_2), 1.22 (d, J = 6.9 Hz, 6H, $CHMe_2$), 1.29 (d, J = 6.9 Hz, 6H, $CHMe_2$), 1.34 (d, J = 6.9

Hz, 6H, CH*Me*$_2$), 1.50 (d, J = 6.7 Hz, 6H, CH*Me*$_2$), 1.56 (s, 1H, C*H*$_2$CMeCH$_2$), 1.75 (s, 1H, C*H*$_2$CMeCH$_2$), 2.68 (d, J = 3.6 Hz, 1H, C*H*$_2$CMeCH$_2$), 3.33-3.57 (m, 4H, C*H*Me$_2$), 3.69 (d, J = 3.1 Hz, 1H, C*H*$_2$CMeCH$_2$), 3.97-4.08 (m, 4H, NC*H*$_2$), 7.25-7.19 (m, 4H, Ar), 7.34 (t, J = 7.7 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 23.7, 23.8, 26.6, 26.7, 28.4, 28.6, 49.5, 53.8, 72.2, 124.3, 124.4, 129.0, 129.7, 136.6, 147.1, 147.3. C.I. MS (relative intensity): 550 (10), 496 (50), 389 (10), 347 (10), 188 (15), 146 (13), 91 (31). HRMS C.I. [M^+], Calcd.: 587.23841. Actual: 587.23643. Anal. Calcd.: C 63.37, H 7.72, N 4.77. Actual: C 63.41, H 7.80, N 4.65. IR (KBr, cm^{-1}) 2962, 2925, 2868, 1448, 1425, 1382, 1363, 1326, 1267, 1240, 1055, 837, 802, 758, 731, 700, 621.



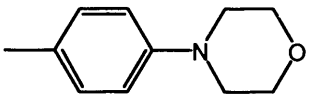
3.2.5. (SIPr)Pd(allyl)Cl.[42] A two-necked flask with a magnetic stirrer was charged with SIPr.HCl (1.9 g, 4.2 mmol) and potassium *tert*-butoxide (0.4 g, 3.6 mmol) and a septum was placed on one neck. The remaining neck was attached to a nitrogen line, after which the flask was cycled with nitrogen and vacuum three times. Under a positive flow of nitrogen, *iso*-propanol (35 mL) was added *via* syringe through the septum and the mixture was stirred for 2 h at 80 °C. After cooling to room temperature over 45 min, the septum was removed, [Pd(allyl)Cl]$_2$ (0.55 g, 1.5 mmol) was added quickly and the septum was replaced. The mixture was stirred for 2 h at room temperature, over which time its colour gradually turned grey. It was then opened to the air and stirred for 15 min. Water (100 mL) was added and a solid

precipitated. Filtration afforded an off-white solid, which was washed with water (4 x 50 mL). It was dried *in vacuo*, affording the desired complex (1.14 g, 1.9 mmol, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (dd, J = 8.8 Hz, 6.9 Hz, 1H), 1.26 (dd, J = 11.5 Hz, 6.9 Hz, 12H), 1.35 (d, J = 6.4 Hz, 6H), 1.45 (d, J = 6.5 Hz, 6H), 2.73 (d, J =13.6 Hz, 1H), 3.01 (d, J = 5.1 Hz, 1H), 3.45 (dq, J = 13.2 Hz, 6.4 Hz, 4H), 3.87 (d, J = 7.4 Hz, 1H), 3.97-4.10 (m, 4H), 4.74 (ddd, J = 18.7 Hz, 13.6 Hz, 7.6 Hz, 1H), 7.17-7.27 (d, m, 4H), 7.33 (t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 23.8, 24.2, 26.6, 28.5, 49.9, 54.0, 114.6, 124.3, 129.1, 136.3, 147.0, 147.3. C.I. MS (relative intensity): HRMS C.I. [M^++H], 1065 (28), 884 (27), 618 (25), 574 (M^+, 27), 536 (62), 391 (100), 338 (64), 188 (57), 97 (49). Calcd.: 575.23841. Actual: 575.23731. Anal. Calcd.: C 62.80, H 7.51, N 4.89. Actual: C62.06, H 7.62, N 4.72. IR (KBr, cm^{-1}) 3074, 2962, 2925, 2868, 1633, 1454, 1427, 1382, 1326, 1267, 1242, 1055, 1020, 999, 804, 758, 732.

3.3. Buchwald-Hartwig Amine Arylation under Pd-NHC catalysis

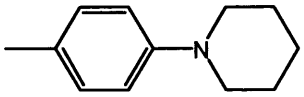
3.3.1 Imidazolium Salt Study

General Procedure: An oven-dried Schlenk tube was charged with an aryl halide (1.0 mmol), an amine (1.2 mmol, 1.2 eq), dipalladium(0) tris(dibenzylidene)acetone (9 mg, 0.01 mmol, 0.02 eq. Pd), 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (17 mg, 0.04 mmol, 0.04 eq) and a magnetic stirrer bar and was sealed with a septum. The flask was evacuated and backfilled with inert gas three times, after which LHMDS (1 M solution in tetrahydrofuran, 1.5 mL, 1.5 mmol, 1.5 eq) was added *via* syringe. The tube was placed in an oil bath maintained at 22 °C, followed by stirring for between 7 and 120 h (reaction times were not optimised). After all of the aryl halide had been consumed, as judged by TLC, the mixture was diluted with ethyl acetate and filtered through a short plug of silica. The solvent was removed *in vacuo* and the crude material was purified *via* flash column chromatography on silica gel using an eluent of ethyl acetate and hexane/petroleum ether.

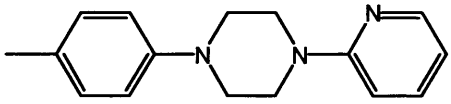


***N*-(4-Methylphenyl)morpholine (Table 12, Entry 1).**[112] The coupling of morpholine and 4-bromotoluene was performed using the general procedure to afford 159 mg (89%) of the title compound within 7 h as an off-white solid (mp 79 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, ArCH_3), 3.13 (t, J = 4.8 Hz, 4H, NCH_2), 3.88 (t, J = 4.8 Hz, 4H, OCH_2), 6.86 (d, J = 8.7 Hz, 2H, Ar), 7.12 (d, J = 8.7 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 50.0, 67.0, 116.1, 129.6, 129.8, 149.3. E.I. MS (relative intensity): 177 (M^+, 18), 119 (100), 103 (8), 91 (30). E.I. HRMS [M^+],

Calcd.: 177.11536. Actual: 177.11547. IR (KBr, cm^{-1}): 2976, 2956, 2912, 2889, 2852, 2831, 2748, 2694, 1515, 1452, 1365, 1298, 1259, 1168, 1118, 1064, 1049, 921, 819.

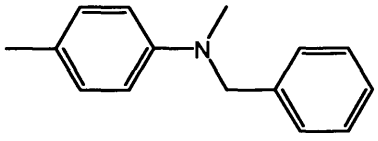


***N*-(4-Methylphenyl)piperidine (Table 12, Entry 2).**[112] The coupling of piperidine and 4-bromotoluene was performed using the general procedure to afford 172 mg (98%) of the title compound within 10 h as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52-1.67 (m, 2H, $N(CH_2)_2CH_2$), 1.75-1.82 (m, 4H, NCH_2CH_2), 2.34 (s, 3H, $ArCH_3$), 3.16 (t, J = 5.3 Hz, 4H, NCH_2), 6.94 (d, J = 8.6 Hz, 2H, Ar), 7.16 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 20.5, 24.4, 26.1, 51.4, 117.05, 128.8, 129.6, 150.4. E.I. MS (relative intensity): 175 (M^+, 88), 174 (M^+-H, 100), 146 (11), 131 (25), 119 (41), 103 (30), 91 (54). E.I. HRMS [M^+], Calcd.: 175.13609. Actual: 175.13578. IR (KBr, cm^{-1}): 2930, 2855, 2797, 1616, 1516, 1450, 1383, 1335, 1234, 1032, 918, 810.

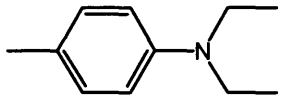


***N*-(4-Methylphenyl)-1-(2-pyridyl)piperazine (Table 12, Entry 3).**[112] The coupling of 1-(2-pyridyl)-piperazine and 4-bromotoluene was performed using the general procedure to afford 160 mg (66%) of the title compound within 24 h as a light yellow solid (mp 96-98 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, $ArCH_3$), 3.25 (t, J = 5.2 Hz, 2H, NCH_2), 3.70 (t, J = 5.2 Hz, 2H, NCH_2), 6.46-6.51 (m, 2H, Ar), 6.91 (d, J = 8.6 Hz, 2H, Ar), 7.11 (d, J = 8.7 Hz, 2H, Ar), 7.45-7.55 (m, 1H, Ar), 8.22-8.24 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 45.4, 49.8, 107.3, 113.6, 116.8, 129.7, 129.7, 137.6, 148.0, 149.2, 159.5. E.I. MS (relative intensity): 253 (M^+, 83), 159 (66),

147 (87), 133 (38), 119 (74), 107 (100), 91 (57), 79 (89). E.I. HRMS [M^+], Calcd.: 253.15789. Actual: 253.15766. IR (KBr, cm^{-1}): 2827, 2709, 1594, 1561, 1519, 1483, 1438, 1390, 1314, 1242, 1210, 1162, 1128, 1099, 1039, 980, 955, 804, 775, 734. Anal. Calcd. for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Actual: C, 75.38; H, 7.69; N, 16.10.

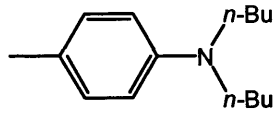


***N,N*-(4-Methylphenyl)methylbenylamine (Table 12, Entry 4).**[112] The coupling of *N*-benzylmethylamine and 4-bromotoluene was performed using the general procedure to afford 154 mg (73%) of the title compound within 24 h as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, ArCH_3) 3.08 (s, 3H, NCH_3), 4.59 (s, 2H, PhCH_2), 6.80 (d, 2H, J = 6.7 Hz, Ar), 7.14 (d, 2H, J = 6.7 Hz, Ar), 7.32-7.43 (m, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 38.7, 57.1, 112.9, 125.9, 126.9, 127.0, 128.6, 129.8, 139.4, 147.9. E.I. MS (relative intensity): 211 (M^+, 41), 134 (32), 120 (15), 91 (100). HRMS E.I. [M^+], Calcd.: 211.13609. Actual: 211.13558. IR (KBr, cm^{-1}): 3062, 3026, 2918, 2860, 2810, 1618, 1570, 1521, 1494, 1475, 1451, 1354, 1325, 1296, 1249, 1210, 1191, 1114, 1074, 1029, 945, 803, 733, 699.

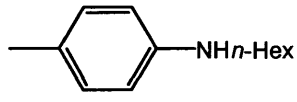


***N*-(4-Methylphenyl)diethylamine (Table 12, Entry 5).**[112] The coupling of diethylamine and 4-bromotoluene was performed using the general procedure to afford 121 mg (74%) of the title compound within 20 h as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 6H, CH_2CH_3), 2.37 (s, 3H, ArCH_3), 3.42 (q, J =

7.1 Hz, 4H, NCH_2), 6.74 (d, J = 8.7 Hz, 2H, Ar), 7.14 (d, J = 8.7 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.7, 20.3, 44.7, 112.7, 124.8, 129.0, 145.9. E.I. MS (relative intensity): 164 (M^++H, 100), 163 (M^+, 92), 162 (M^+-H, 18) 148 (17). HRMS E.I. [M^++H], Calcd.: 164.14392. Actual: 164.14412. IR (KBr, cm^{-1}): 2969, 2928, 2868, 1619, 1570, 1521, 1465, 1450, 1394, 1374, 1356, 1264, 1196, 1151, 1094, 1074, 1012, 801, 783.

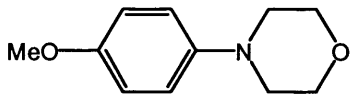


***N*-(4-Methylphenyl)di-*n*-butylamine (Table 12, Entry 6).**[112] The coupling of di-*n*-butylamine and 4-bromotoluene was performed using the general procedure except with 3 mol% $Pd_2(dba)_3$ and 12 mol% SIPr.HCl to afford 37 mg (17%) of the title compound within 5 days as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.6 Hz, 6H, $(CH_2)_3CH_3$), 1.25-1.45 (m, 8H, $NCH_2(CH_2)_2$), 2.30 (s, 3H, ArCH_3), 3.37 (q, J = 7.6 Hz, 4H, NCH_2), 6.60 (d, J = 8.6 Hz, 2H, Ar), 7.04 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.2, 20.4, 29.5, 51.0, 112.2, 124.4, 129.7, 146.2. E.I. MS (relative intensity): 218 (40), 204 (76), 188 (82), 172 (22), 158 (12), 146 (60), 130 (26), 118 (51), 97 (47), 91 (20). HRMS E.I. [M^++H], Calcd.: 220.20651. Actual: 220.20620. IR (KBr, cm^{-1}): 2957, 2930, 2866, 2361, 2332, 1618, 1518, 1460, 1367, 1290, 1221, 1184, 1148, 1103, 1016, 930, 800, 752.



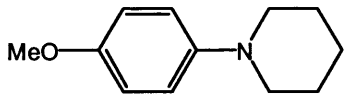
***N*-(4-Methylphenyl)*n*-hexylamine (Table 12, Entry 7).**[112] The coupling of *n*-hexylamine and 4-bromotoluene was performed using the general procedure except with 2 mol% $Pd_2(dba)_3$ and 8 mol% SIPr.HCl and 3.6 eq of amine at 80 °C to afford

116 mg (61%) of the title compound within 24 h as a white crystalline solid (mp: 49 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 3H, $(CH_2)_5CH_3$), 1.25-1.50 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.26 (s, 3H, $ArCH_3$), 3.10 (t, J = 7.6 Hz, 2H, NCH_2), 3.20-3.50 (br s, 1H, N*H*), 6.75 (d, J = 8.6 Hz, 2H, Ar), 7.01 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.1, 20.4, 22.7, 26.9, 29.6, 31.7, 44.5, 113.0, 126.3, 129.7, 146.3. E.I. MS (relative intensity): 192 (M^++H, 20), 191(M^+, 95), 120 (100). HRMS E.I. [M^+], Calcd.: 191.16739. Actual: 191.16745. IR (KBr, cm^{-1}): 2924, 2855, 1616, 1522, 1470, 1313, 1254, 1223, 1182, 1126, 1042, 806, 729. ***N,N*-bis(4-methylphenyl)*n*-hexylamine.** The reaction also afforded 21 mg (15%) of the bisarylation product within 24 h as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90-1.00 (m, 3H, $(CH_2)_5CH_3$), 1.25-1.45 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.33 (s, 6H, $ArCH_3$), 3.66 (t, J = 7.7 Hz, 2H, NCH_2), 6.91 (d, J = 8.6 Hz, 4H, Ar), 7.09 (d, J = 8.6 Hz, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.6, 22.7, 26.9, 27.5, 31.7, 52.5, 120.9, 129.8, 130.2, 146.1. E.I. MS (relative intensity): 282 (M^++H, 100), 281 (M^+, 72), 211 (62), 210 (98), 196 (30), 180 (48), 118 (88), 91 (49). HRMS E.I. [M^+], Calcd.: 281.21434. Actual: 281.21437. IR (KBr, cm^{-1}): 2926, 2860, 1612, 1510, 1458, 1367, 1252, 1188, 1136, 1080, 1043, 808.

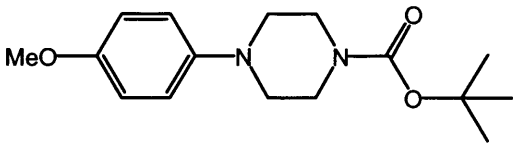


***N*-(4-Methoxyphenyl)morpholine (Table 12, Entry 8).**[112] The coupling of morpholine and 4-bromoanisole was performed using the general procedure to afford 151 mg (78%) of the title compound within 24 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.03-3.07 (m, 4H, OCH_2), 3.77 (s, 3H, OCH_3), 3.84-3.87 (m, 4H, NCH_2), 6.83-6.94 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 50.8, 55.6, 67.1, 114.5, 117.8, 145.7,

154.0. E.I. MS (relative intensity): 193 (M^+, 100), 178 (25), 135 (100), 120 (83), 92 (12). HRMS EI [M^+], Calcd.: 193.11027. Actual: 193.11000. IR (KBr, cm^{-1}): 2934, 2853, 2831, 2802, 1510, 1464, 1454, 1442, 1385, 1292, 1244, 1182, 1132, 1042, 1028, 824.

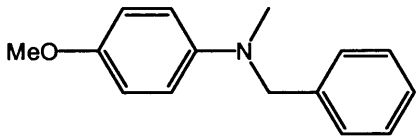


***N*-(4-Methoxyphenyl)piperidine (Table 12, Entry 9).**[112] The coupling of piperidine and 4-bromoanisole was performed using the general procedure to afford 168 mg (88%) of the title compound within 24 h as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52-1.60 (m, 2H, $(CH_2)_2CH_2$), 1.70-1.78 (m, 4H, NCH_2CH_2), 3.04 (t, J = 5.4 Hz, 4H, NCH_2), 3.77 (s, 3H, OCH_3), 6.84 (d, J = 9.1 Hz, 2H, Ar), 6.93 (d, J = 9.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 26.2, 52.3, 55.5, 114.3, 118.8, 146.9, 153.6. E.I. MS (relative intensity): 191 (M^+, 13), 135 (100), 92 (8). HRMS E.I. [M^+], Calcd.: 191.13047. Actual: 191.12980. IR (KBr, cm^{-1}): 2933, 2792, 1511, 1463, 1452, 1442, 1383, 1292, 1233, 1217, 1181, 1121, 1041, 1027, 919, 861, 823, 795.

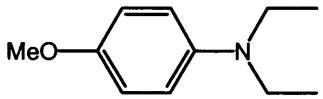


***N*-(4-Methoxyphenyl)-*N'*-Boc-piperazine (Table 12, Entry 10).**[112] The coupling of *N*-Boc-piperazine and 4-bromoanisole was performed using the general procedure to afford 251 mg (86%) of the title compound within 20 h as a white solid (mp: 97 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, CMe_3), 3.01 (t, J = 5.3 Hz, Boc-NCH_2), 3.57 (t, J = 5.3 Hz, $PhNCH_2$), 3.76 (s, 3H, OCH_3), 6.82- 6.88 (m, 2H, Ar), 6.89-6.94 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 51.0, 55.6, 79.8, 114.5, 118.9,

146.3, 154.8, 155.5. E.I. MS (relative intensity): 292 (M^+, 35), 236 (78), 221 (15), 192 (41), 150 (100), 135 (27), 120 (30), 92 (8). HRMS E.I. [M^+], Calcd.: 292.17814. Actual: 292.17827.

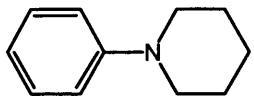


***N,N*-(4-Methoxyphenyl)methylbenylamine (Table 12, Entry 11).**[112] The coupling of *N*-benzylmethylamine and 4-bromoanisole was performed using the general procedure to afford 171 mg (75%) of the title compound within 48 h as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 3H, ArCH_3), 3.87 (s, 3H, CH_3O), 4.55 (s, 2H, PhCH_2), 6.89 (d, 2H, J = 9.0 Hz, *Ar*N), 6.97 (d, 2H, J = 9.0 Hz, *Ar*N), 7.34-7.48 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.2, 55.8, 58.1, 127.0, 127.3, 128.6, 139.4, 145.0, 152.0. E.I. MS (relative intensity): 227 (M^+, 100), 193 (4), 150 (22), 136 (100), 121 (12), 91 (76). HRMS E.I. [M^+], Calcd.: 227.13101. Actual: 227.13079. IR (KBr, cm^{-1}): 2903, 2831, 2804, 1516, 1452, 1360, 1296, 1246, 1180, 1115, 1038, 1001, 943, 905, 816, 737, 702.

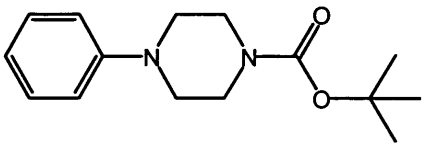


***N*-(4-Methoxyphenyl)diethylamine (Table 12, Entry 12).**[112] The coupling of diethylamine and 4-bromoanisole was performed using the general procedure to afford 96 mg (54%) of the title compound within 72 h as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 6H, J = 7.1 Hz, CH_2CH_3), 3.29 (q, 4H, J = 7.1 Hz, NCH_2), 3.79 (s, 3H, OCH_3), 6.74 (d, 2H, J = 9.1 Hz, Ar), 6.86 (d, 2H, J = 9.1 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5, 45.3, 55.8, 114.8, 115.3, 142.9, 151.6. E.I. MS

(relative intensity): 179 (M^+, 35), 164 (100), 136 (12). HRMS E.I. [M^+], Calcd.: 179.13101. Actual: 179.13039. IR (KBr, cm^{-1}): 3044, 2969, 2932, 2831, 1618, 1577, 1513, 1465, 1447, 1374, 1357, 1243, 1197, 1182, 1151, 1093, 1074, 1042, 1014, 813, 781, 667.

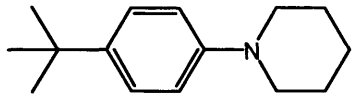


***N*-Phenylpiperidine (Table 12, Entry 13).**[112] The coupling of piperidine and bromobenzene was performed using the general procedure to afford 143 mg (89%) of the title compound within 20 h as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ1.57-1.63 (m, 2H, $N(CH_2)_2CH_2$), 1.70-1.78 (m, 4H, NCH_2CH_2), 3.18 (t, J = 5.4 Hz, 4H, NCH_2), 6.85 (dt, 1H, J = 7.3 Hz, Ar), 6.97 (dd, 2H, J = 7.3 Hz, Ar), 7.28 (dt, 2H, J = 7.3 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 25.9, 50.7, 116.6, 119.2, 129.0, 152. E.I. MS (relative intensity): 161 (M^+, 80), 160 (100), 137 (20), 120 (40), 95 (41). HRMS EI [M^+], Calcd.: 161.12044. Actual: 161.12017. IR (KBr, cm^{-1}): 3028, 2932, 2799, 2704, 1923, 1678, 1599, 1497, 1450, 1381, 1337, 1231, 1126, 1072, 1030, 991, 959, 918, 864, 814, 754, 692.

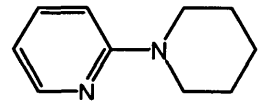


***N*-(Phenyl)-*N'*-Boc-piperazine (Table 12, Entry 14).**[112] The coupling of 1-boc-piperazine and bromobenzene was performed using the general procedure to afford 231 mg (88%) of the title compound within 20 h as a white solid (mp: 72 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 9H, CMe_3), 3.12 (t, 4H, J = 5.2 Hz, Boc-NCH_2), 3.48 (t, 4H, J = 5.2 Hz, $PhNCH_2$), 6.83-6.94 (m, 3H, Ar), 7.24-7.29 (m, 2H, Ar). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 28.1, 49.6, 79.9, 116.2, 120.2, 138.7, 151.3, 154.8. E.I. MS (relative intensity): 262 (M^+, 68), 206 (100), 189 (22), 162 (31), 132 (88), 120 (100), 105 (54), 91 (33). HRMS E.I. [M^+], Calcd.: 262.16758. Actual: 262.16783.

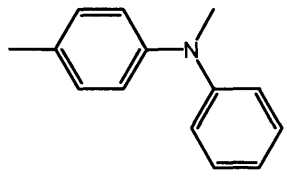


***N*-(4-*tert*-butylphenyl)piperidine (Table 12, Entry 15).**[112] The coupling of piperidine and 4-*tert*-butylbromobenzene was performed using the general procedure to afford 39 mg (18%) of the title compound within 96 h as a white solid (mp 37 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 9H, CH_3), 1.53-1.60 (m, 2H, $NCH_2CH_2CH_2$), 1.68-1.76 (m, 4H, NCH_2CH_2), 3.13 (t, J = 5.5 Hz, 4H, NCH_2), 6.91 (d, 2H, J = 8.9 Hz, Ar), 7.29 (d, 2H, J = 8.9 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 26.0, 31.5, 33.9, 50.9, 116.3, 125.8, 142.0, 150.0. E.I. MS (relative intensity): 217 (M^+, 28), 202 (100), 149 (5). HRMS E.I. [M^+], Calcd.: 217.18304. Actual: 217.18314. IR (KBr, cm^{-1}): 2930, 2805, 2708, 1608, 1516, 1447, 1382, 1361, 1235, 1218, 1201, 1156, 1127, 1028, 920, 819.

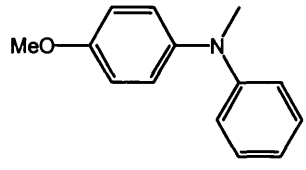


***N*-(2-pyridyl)piperidine (Table 12, Entry 16).**[112] The coupling of piperidine and 2-bromopyridine was performed using the general procedure to afford 119 mg (73%) of the title compound after 48 h as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 6H, $NCH_2(CH_2)_3$), 3.50 (s, 4H, NCH_2), 6.53-6.55 (m, 1H, Ar), 6.62 (d, J = 8.6 Hz, 1H, Ar), 7.39-7.45 (m, 1H, Ar), 8.15-8.17 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 25.5, 46.3, 107.1, 112.4, 137.3, 147.9, 159.7. E.I. MS (relative intensity): 162

(60), 146 (10), 133 (63), 119 (42), 107 (50), 94 (23), 84 (100). HRMS E.I. [M^+], Calcd.: 162.11569. Actual: 162.11518. IR (KBr, cm^{-1}): 2999, 2932, 2853, 2818, 1595, 1485, 1439, 1383, 1312, 1246, 1161, 1130, 1024, 978, 932, 853, 772, 733.



***N,N*-(4-methylphenyl)methylaniline (Table 12, Entry 17).**[112] The coupling of *N*-methylaniline and 4-bromotoluene was performed using the general procedure except with 2 mol% $Pd_2(dba)_3$ and 8 mol% SIPr.HCl. This gave 194 mg (98%) of the title compound within 48 h as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, ArCH_3), 3.40 (s, 3H, NCH_3), 6.96-7.38 (m, 9H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 40.4, 118.3, 119.9, 122.7, 129.2, 130.1, 132.1, 146.7, 149.5. E.I. MS (relative intensity): 197 (M^+, 100), 167 (14), 149 (8), 106 (12), 91 (27), 77 (22). HRMS E.I. [M^+], Calcd.: 197.12044. Actual: 197.12090. IR (KBr, cm^{-1}): 3028, 2870, 2808, 1570, 1504, 1456, 1339, 1256, 1124, 1080, 1030, 868, 818, 752, 694.



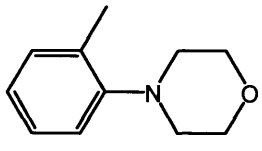
***N,N*-(4-methoxyphenyl)methylaniline (Table 12, Entry 18).**[112] The coupling of *N*-methylaniline and 4-bromoanisole was performed using the general procedure except with 2 mol% $Pd_2(dba)_3$ and 8 mol% SIPr.HCl. This gave 177 mg (83%) of the title compound within 72 h as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (s, 3H, NCH_3), 3.86 (s, 3H, CH_3O), 6.86 (d, J = 7.2 Hz, 3H, Ar), 6.95 (d, J = 8.8 Hz, 2H, Ar), 7.16 (d, J = 8.8 Hz, 2H, Ar), 7.26 (t, J = 7.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$):

δ 40.6, 55.6, 114.9, 115.8, 118.4, 126.3, 129.0, 142.3, 149.8, 156.4. E.I. MS (relative intensity): 213 (M^+, 78), 198 (100), 183 (6), 154 (11), 129 (8), 103 (7), 91 (6). HRMS E.I. [M^+], Calcd.: 213.11536. Actual: 213.11560. IR (KBr, cm^{-1}): 3006, 2953, 2834, 1598, 1501, 1354, 1283, 1237, 1182, 1130, 1104, 1031, 1009, 870, 837, 792, 749, 732.

3.3.2. Study with Isolated Pd-NHC Complex

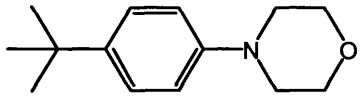
General Procedure: An oven-dried Schlenk tube was charged with an aryl halide (1.0 mmol), an amine (1.2 mmol, 1.2eq.), the Pd-NHC complex (18 mg, 0.03 mmol, 3.0 mol%) and a magnetic stirrer bar and was sealed with a septum. The flask was evacuated and backfilled with inert gas three times, after which LHMDS (1M solution in tetrahydrofuran) was added *via* syringe. The bottom of the tube was then placed in an oil bath maintained at 22 °C, followed by stirring until the aryl halide had been consumed, as judged by TLC. The mixture was diluted with ethyl acetate and filtered through a short plug of silica. The solvent was removed *in vacuo* and the crude material was purified *via* flash chromatography on silica gel using an eluent of ethyl acetate with hexane or petroleum ether.

Additional Spectra from Morpholine Study

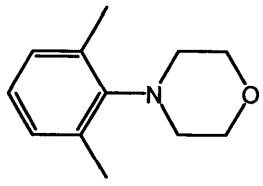


***N*-(2-methylphenyl)morpholine (Table 13, Entry 1).**[112] The coupling of morpholine and 2-bromotoluene was performed using the general procedure to afford 175 mg (99%) of the title compound within 1 min as a yellow oil. ^1H NMR (300 MHz,

$CDCl_3$): δ 2.33 (s, 3H, ArCH_3), 2.89-2.95 (m, 2H, NCH_2), 3.79-3.91 (m, 2H, OCH_2), 6.97-7.06 (m, 2H, Ar), 7.14-7.24 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 52.3, 67.5, 119.0, 123.5, 126.7, 131.2, 132.7, 151.4. E.I. MS (relative intensity): 204 (10), 177 (M^+, 50), 119 (100), 118 (53). HRMS E.I. [M^+], Calcd.: 177.11482. Actual: 177.11425. IR (KBr, cm^{-1}): 2957, 2853, 2816, 1599, 1491, 1450, 1373, 1298, 1254, 1225, 1117, 1043, 934, 762.



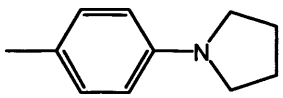
***N*-(4-*tert*-butylphenyl)morpholine (Table 13, Entry 4).**[112] The coupling of morpholine and 4-*tert*-butylbromobenzene was performed using the general procedure to afford 199 mg (91%) of the title compound as a colourless oil within 5 min as a white solid (mp: 59-62 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 9H, CMe_3), 3.09-3.22 (m, 4H, NCH_2), 3.81-3.95 (m, 4H, OCH_2), 6.89-6.97 (d, 2H, Ar), 7.32-7.41 (d, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 34.0, 49.6, 67.0, 115.5, 126.0, 142.8, 149.0. E.I. MS (relative intensity): 219 (M^+, 85), 204 (100). HRMS EI [M^+], Calcd.: 219.16177. Actual: 219.16209. IR (KBr, cm^{-1}): 2976, 2835, 1519, 1450, 1363, 1299, 1261, 1176, 1120, 1070, 925, 819, 734, 553.



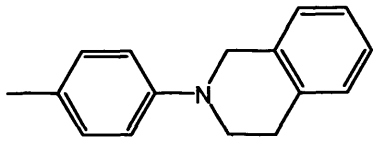
***N*-(2,6-dimethylphenyl)morpholine (Table 13, Entry 9).**[41] The coupling of morpholine and 2,6-dimethylchlorobenzene was performed using the general procedure to afford 46 mg (24%) of the title compound within 60 min as a colourless crystalline solid (mp: 94 °C). The coupling was repeated using the general procedure

at 70 °C to afford 99 mg (52%) of the title compound within 10 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H, ArCH_3), 3.07-3.14 (m, 4H, NCH_2), 3.78-3.85 (m, 4H, OCH_2), 6.95-7.04 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 50.0, 68.2, 125.4, 129.1, 137.0, 147.9. E.I. MS (relative intensity): 246 (25), 191 (M^+, 82), 190 (100), 188 (61), 146 (65), 133 (95), 132 (74), 117 (28), 86 (47), 84 (81). HRMS EI [M^+], Calcd.: 191.13047; Actual: 191.13139. IR (KBr, cm^{-1}): 2966, 2848, 2813, 2732, 2682, 1613, 1471, 1438, 1369, 1259, 1209, 1109, 1041, 937, 842, 781, 738, 673, 505.

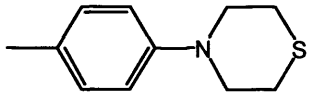
Additional Spectra from Study of Secondary Amines:



***N*-(4-methylphenyl)pyrollidine (Table 14, Entry 5).**[112] The coupling of pyrollidine and 4-bromotoluene was performed using the general procedure to afford 64 mg (40%) of the title compound within 5 min as a colourless oil. The reaction would not go to completion. The coupling of pyrollidine and 4-bromotoluene was repeated using the general procedure except at 70 °C to afford 135 mg (84%) of the title compound within 2 min as a yellow solid (mp: 46 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99-2.09 (m, 4H, NCH_2CH_2), 2.33 (s, 3H, ArCH_3), 3.32 (t, J = 4.7 Hz, 4H, NCH_2), 6.55-6.59 (m, 2H, Ar), 7.09-7.15 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 25.5, 47.9, 111.9, 124.5, 129.7, 146.2. E.I. MS (relative intensity): 161 (M^+, 100), 160 (54), 105 (37), 86 (55). HRMS EI [M^+], Calcd.: 161.11990. Actual: 161.1928. IR (KBr, cm^{-1}): 3012, 2964, 2854, 1622, 1564, 1521, 1487, 1460, 1367, 1346, 1278, 1244, 1186, 1159, 802, 509.

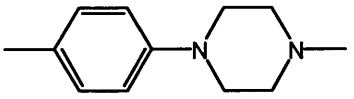


***N*-(4-methylphenyl)-1,2,3,4-tetrahydroisoqunioline (Table 14, Entry 6).** The coupling of 1,2,3,4-tetrahydroisoqunioline and 4-bromotoluene was performed using the general procedure to afford 145 mg (65%) of the title compound within 30 min as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, ArC*H*$_3$), 3.00 (t, *J* = 5.9 Hz, 2H, NCH$_2$C*H*$_2$), 3.53 (t, *J* = 5.9 Hz, 2H, NC*H*$_2$CH$_2$), 4.38 (s, 2H, NC*H*$_2$Ar), 6.93-6.96 (m, 2H, Ar), 7.06-7.21 (m, 6H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 29.1, 47.3, 51.5, 115.9, 126.0, 126.6, 128.4, 128.6, 129.6, 134.6, 134.8, 148.7. E.I. MS (relative intensity): 237 (70), 223 (M^+, 75), 222 (40), 119 (25), 118 (100), 104 (37), 91 (48), 90 (57). HRMS EI [M^+], Calcd.: 223.13555. Actual: 223.13458. IR (KBr, cm^{-1}): 3030, 2920, 2864, 1659, 1602, 1581, 1473, 1458, 1406, 1329, 1309, 1253, 1228, 1168, 813, 761, 742.

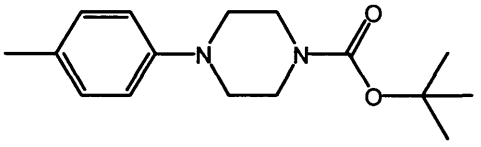


***N*-(4-methylphenyl)thiomorpholine (Table 14, Entry 8).** The coupling of thiomorpholine and 4-bromotoluene was performed using the general procedure to afford 116 mg (60%) of the title compound within 10 min as a colourless solid (mp: 40 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, ArC*H*$_3$), 2.75-2.79 (m, 4H, SC*H*$_2$), 3.46-3.49 (m, 4H, NC*H*$_2$), 6.85 (d, *J* = 8.8 Hz, 2H, Ar), 7.08 (d, *J* = 8.8 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 27.2, 52.8, 117.7, 129.6, 129.8, 149.6. E.I. MS (relative intensity): 193 (M^+, 54), 119 (100). HRMS E.I. [M^+], Calcd.: 193.09197. Actual: 193.09170. IR (KBr, cm^{-1}): 2954, 2908, 2873, 2827, 2754, 1616,

1573, 1514, 1450, 1415, 1336, 1290, 1224, 1193, 1168, 1136, 1029, 970, 893, 819, 530.

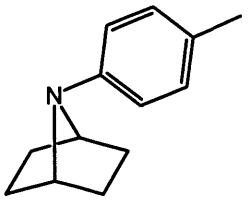


***N*-(4-methylphenyl)-*N'*-methylpiperazine (Table 14, Entry 9).** The coupling of *N*-methylpiperazine and 4-bromotoluene was performed using the general procedure to afford 153 mg (80%) of the title compound within 5 min as a colourless solid (mp: 75 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, NCH_3), 2.36 (s, 3H, ArCH_3), 2.58 (t, J = 5.1 Hz, 4H, MeNCH_2), 3.17 (t, J = 5.1 Hz, 4H, ArNCH_2), 6.84-6.88 (m, 2H, Ar), 7.18-7.22 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 27.2, 46.2, 49.7, 55.2, 116.4, 129.1, 129.7, 149.3. E.I. MS (relative intensity): 190 (M^+, 100), 146 (18), 119 (63). HRMS E.I. [M^+], Calcd.: 190.14645. Actual: 190.1492. IR (KBr, cm^{-1}): 2964, 2937, 2918, 2837, 2790, 2748, 2700, 1616, 1515, 1452, 1379, 1336, 1294, 1267, 1242, 1211, 1159, 1078, 1008, 921, 812, 736, 526.

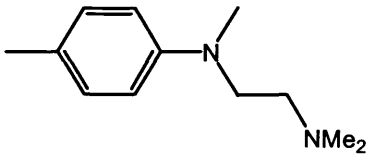


***N*-(4-methylphenyl)-*N'*-Boc-morpholine (Table 14, Entry 10).** The coupling of *N*-Boc-piperazine and 4-bromotoluene was performed using the general procedure to afford 264 mg (96%) of the title compound within 5 min as a white crystalline solid (mp: 105 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (s, 9H, CMe_3), 2.23 (ArCH_3), 3.07 (t, J = 5.2 Hz, 4H, Boc-NCH_2), 3.57 (t, J = 5.2 Hz, 4H, ArNCH_2), 6.84 (d, J = 8.5 Hz, 2H, Ar), 7.08 (d, J = 8.5 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 28.5, 50.0, 117.0, 129.7, 149.2, 154.8. C.I. MS (relative intensity): 277 (M^++H, 34), 221 (100), 159 (14). HRMS C.I. [M^++H], Calcd.: 277.19160. Actual: 277.19112. IR (KBr, cm^{-1}):

2976, 2868, 2815, 1681, 1515, 1477, 1417, 1390, 1363, 1346, 1265, 1236, 1207, 1159, 1122, 1003, 925, 817, 738, 704.

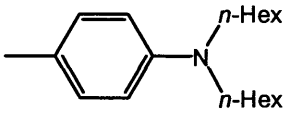


7-(4-Tolyl)-7-azabicyclo[2.2.1]heptane (Table 14, Entry 11).[113] The coupling of 7-azabicyclo[2.2.1]heptane hydrochloride and 4-bromotoluene was performed using the general procedure at 70 °C and with 2.4 mL LHMDS (2.4 mmol, 2.4 eq) to afford 16 mg (9%) of the title compound within 3 h as a white solid (mp: 175 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37-1.45 (m, 4H, CH_2CH_2), 1.77-1.80 (m, 4H, CH_2CH_2), 2.25 (s, 3H, $ArCH_3$), 4.17 (m, 2H, NCH_2), 6.82 (d, J = 8.2 Hz, 2H, Ar), 7.00 (d, J = 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 28.7, 58.1, 116.5, 128.2, 129.6, 145.7. C.I. MS (relative intensity): 216 (7), 189 (12), 188 (M^++H, 100), 187 (M^+, 70), 186 (M^+-1, 14), 158 (16). HRMS C.I. [M^++H], Calcd.: 188.14392. Actual: 188.14448. IR (KBr, cm^{-1}): 2962, 2868, 1514, 1454, 1384, 1329, 1261, 1145, 1047, 956.

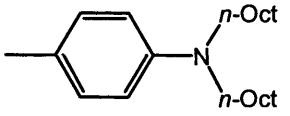


***N*-(4-methylphenyl)-*N,N',N'*-trimethyl-1,2-diaminoethane (Table 14, Entry 13).** The coupling of *N,N,N'*-trimethyl-1,2-diaminoethane and 4-bromotoluene was performed using the general procedure to afford 73 mg (38%) of the title compound within 18 h as a yellow oil. The coupling of *N,N,N'*-trimethyl-1,2-diaminoethane and 4-bromotoluene was repeated using the general procedure at 70 °C to afford 163 mg (85%) of the title compound within 5 h as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, $ArCH_3$), 2.30 (s, 6H, NMe_2), 2.46-2.52 (m, 2H, Me_2NCH_2), 2.93 (s, 3H,

ArN*Me*), 3.37-3.46 (m, 2H, ArN(Me)CH_2), 6.68 (d, J = 8.3 Hz, 2H, Ar), 7.05 (d, J = 8.3 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 38.8, 45.9, 51.4, 55.9, 112.6, 125.6, 129.8, 147.2. E.I. MS (relative intensity): 192 (M^+, 47), 135 (30), 134 (100), 120 (20), 119 (25), 118 (13), 91 (47), 86 (71). HRMS E.I. [M^++H], Calcd.: 192.16210. Actual: 192.16241. IR (KBr, cm^{-1}): 2941, 2860, 2818, 2768, 1620, 1522, 1462, 1366, 1250, 1180, 1115, 1042, 961, 802.

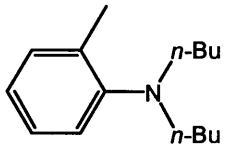


***N*-(4-methylphenyl)di-*n*-hexylamine (Table 14, Entry 15).** The coupling of di-*n*-hexylamine and 4-bromotoluene was performed using the general procedure at 70 °C to afford 270 mg (98%) of the title compound within 1 h as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 1.09 (t, J = 6.3 Hz, 6H, $(CH_2)_5CH_3$), 1.49 (br s, 12H, $NCH_2CH_2(CH_2)_3$), 1.72-1.76 (m, 4H, NCH_2CH_2), 2.37 (s, 3H, $ArCH_3$), 3.40 (t, J = 7.6 Hz, 4H, NCH_2), 6.75 (d, J = 8.6 Hz, 2H, Ar), 7.19 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.2, 22.7, 26.9, 27.3, 31.8, 51.4, 112.3, 124.5, 129.7, 146.2. E.I. MS (relative intensity): 281 (16), 275 (M^+, 6), 204 (20), 134 (27), 120 (100), 91 (14), 78 (14). HRMS E.I. [M^+], Calcd.: 275.26075. Actual: 275.26094. IR (KBr, cm^{-1}): 2955, 2928, 2858, 1620, 1520, 1466, 1369, 1292, 1254, 1188, 1109, 800.



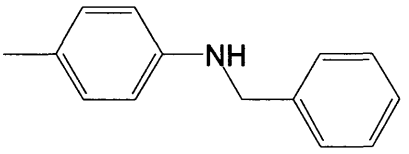
***N*-(4-methylphenyl)di-*n*-octylamine (Table 14, Entry 16).** The coupling of di-*n*-butylamine and 4-bromotoluene was performed using the general procedure at 70 °C to afford 273 mg (86%) of the title compound within 1 h as a yellow oil. ^{1}H NMR

(300MHz, $CDCl_3$): δ 0.97 (t, J = 7.0 Hz, 6H, $(CH_2)_7CH_3$), 1.33-1.38 (br s, 20H, $NCH_2CH_2(CH_2)_5$), 1.61-1.66 (m, 4H, NCH_2CH_2), 2.32 (s, 3H, $ArCH_3$), 3.29 (t, J = 7.6 Hz, 4H, NCH_2), 6.64 (d, J = 8.6 Hz, 2H, Ar), 7.08 (d, J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 20.2, 22.8, 27.4, 29.5, 29.6, 30.4, 32.0, 51.4, 112.2, 124.3, 129.8, 146.3. E.I. MS (relative intensity): 480 (14), 479 (23), 331 (M^+, 55), 233 (29), 232 (100), 134 (65) 120 (19). HRMS E.I. [M^+], Calcd.: 331.32335. Actual: 331.32269. IR (KBr, cm^{-1}): 3009, 2924, 2855, 1620, 1520, 1464, 1393, 1367, 1234, 1186, 1111, 800, 723.

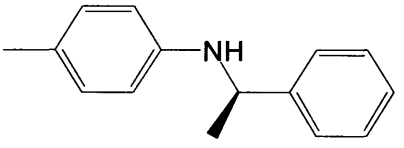


***N*-(4-methylphenyl)di-*n*-butylamine (Table 14, Entry 19).**[40] The coupling of of di-*n*-butylamine and 2-bromotoluene was performed using the general procedure at 70 °C to afford 44 mg (20%) of the title compound within 90 min as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 6H, $(CH_2)_3CH_3$), 1.22-1.42 (m, 8H, $NCH_2(CH_2)_2$), 2.29 (s, 3H, $ArCH_3$), 2.90 (t, J = 7.1 Hz, 4H, NCH_2), 6.93-6.99 (m, 1H, Ar), 7.06-7.18 (m, 3H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.3, 20.5, 53.7, 122.1, 123.0, 125.9, 130.8, 135.0, 150.7. E.I. MS (relative intensity): 219 (M^+, 11), 176 (100), 134 (42), 120 (48), 91 (41). HRMS E.I. [M^+], Calcd.: 219.19815. Actual: 219.19847. IR (KBr, cm^{-1}): 2960, 2931, 2869, 1616, 1539, 1456, 1382, 1363, 1326, 1261, 1056, 804.

Additional Spectra from Primary Amines Study

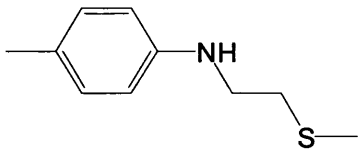


***N*-(4-methylphenyl)benzylamine (Table 15, Entry 2).** The coupling of benzylamine and 4-bromotoluene was performed using the general procedure at 70 °C and with 4.0 eq of amine to afford 79 mg (40%) of the title compound within 30 min as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, ArC*H*$_3$), 3.92 (br s, 1H, N*H*), 4.36 (s, 2H, NC*H*$_2$Ph), 6.62 (d, J = 8.2 Hz, 2H, Ar), 7.05 (d, J = 8.2 Hz, 2H, Ar), 7.35-7.45 (m, 5H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 48.7, 113.1, 126.8, 127.2, 127.6, 128.7, 129.8, 139.8, 146.0. E.I. MS (relative intensity): 197 (M^+, 100), 196 (44), 91 (90). HRMS E.I. [M^+], Calcd.: 197.11990. Actual: 197.11944. IR (KBr, cm^{-1}): 3416, 3028, 2918, 2862, 1618, 1520, 1495, 1470, 1321, 1302, 1265, 1250, 1182, 1126, 808, 743, 723, 698.



***N*-(4-methylphenyl)-1-phenylethylamine (Table 15, Entry 3).** The coupling of (*R*)-(+)-1-phenylethylamine and 4-bromotoluene was performed using the general procedure at 70 °C and with 4.0 eq of amine to afford 148 mg (70%) of the title compound within 30 min as a yellow solid (mp: 70 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (d, J = 6.7 Hz, 3H, NCHC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), 3.95 (br s, 1H, N*H*), 4.51 (q, J = 6.7 Hz, 1H, NC*H*), 6.49 (d, J = 8.4 Hz, 2H, Ar), 6.96 (d, J = 8.4 Hz, 2H, Ar), 7.25-7.30 (m, 1H, Ar), 7.36-7.44 (m, 4H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4,

25.1, 53.7, 113.5, 125.9, 126.4, 126.9, 128.7, 129.7, 145.1, 145.5. E.I. MS (relative intensity): 211 (M^+, 50), 196 (100), 107 (18), 105 (34). HRMS E.I. [M^+], Calcd.: 211.15550. Actual: 211.13497. IR (KBr, cm^{-1}): 3409, 2967, 2862, 1618, 1519, 1488, 1448, 1357, 1317, 1298, 1255, 1205, 1182, 1143, 1066, 1012, 806, 756, 702, 574, 509.



***N*-(4-methylphenyl)-2-(Methylthio)ethylamine (Table 15, Entry 4).** The coupling of 2-(methylthio)ethylamine and 4-bromotoluene was performed using the general procedure at 70 °C and with 4.0 eq of amine to afford 25 mg (14%) of the title compound within 1 h as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, SCH_3), 2.25 (s, 3H, $ArCH_3$), 2.76 (t, J = 6.4 Hz, 2H, NCH_2CH_2S), 3.34 (t, J = 6.4 Hz, 2H, NCH_2), 3.90 (br s, 1H, N*H*), 6.58 (d, J = 8.4 Hz, 2H, Ar), 7.00 (d, J = 8.4 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 20.4, 33.7, 42.3, 113.4, 127.1, 129.8, 145.5. E.I. MS (relative intensity): 181 (M^+, 14), 120 (100), 91 (8), 86 (13). HRMS E.I. [M^+], Calcd.: 181.09197. Actual: 181.09131. IR (KBr, cm^{-1}): 2960, 2916, 2866, 1618, 1519, 1425, 1319, 1257, 1045, 808.

4. References & Notes.

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